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American Heart Journal

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Original Communications

ON EINTHOVEN'S TRIANGLE, THE THEORY OF UNIPOLAR ELECTROCARDIOGRAPHIC LEADS, AND THE INTERPRETATION OF THE PRECORDIAL ELECTROCARDIOGRAM

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EINTHOVEN'S TRIANGLE

IN 1913, Einthoven, Fahr, and de Waart[1] published a method of estimating the direction and manifest magnitude, at a given instant in the cardiac cycle, of that component of the heart's electromotive force which is parallel to the plane defined by the standard limb leads. They utilized this method to study and to explain the modifications of the electrocardiographic deflections of these leads produced by respiratory variations in the position of the heart. The chief purpose which they had in mind seems to have been to find a way of distinguishing electrocardiographic phenomena due to extrinsic causes of this sort from those originating within the heart itself. More than thirty years have passed since this fundamental paper by Einthoven and his associates was written. No other has had so great an effect upon the development of our knowledge of the electrocardiogram; none has been the source of more inspiration; and none has been the subject of so much misunderstanding, so much critical examination, and so much controversial discussion. Why after all these years should there still be a wide difference of opinion regarding the correctness of the views expressed in this paper?

Unlike Einthoven and Fahr, the vast majority of those who have been engaged in the study of the human electrocardiogram have had small acquaintance

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with, and little interest in, mathematical attacks upon physical problems of the sort encountered in attempts to apply the classical theory of electricity to the analysis of the varying electrical field associated with the heartbeat. In theoretical investigations of this kind the actual situation under consideration is always far more complicated than any of those that can be treated mathematically, and it is necessary to make many simplifying assumptions that are not strictly in accord with the facts. To assert that all deductions based on such assumptions are *ipso facto* worthless is, so to speak, to deny that mathematics has contributed anything worth while to the physical sciences. To maintain, on the other hand, that deductions of this kind represent anything more than a first approximation to the truth or have any great value except in so far as they are supported by experience and by experiments designed to test their validity would be equally unreasonable. It is imperative that those who make use of conclusions of this sort as a guide to further investigations, or who attempt to extend them, clearly understand and constantly bear in mind the postulates upon which they rest.

Most of the controversies to which Einthoven's work has given rise seem to have originated in differences between the participants in respect to their familiarity with and their attitude toward its theoretical background. In our opinion, there is no reason to suppose either that Einthoven and his associates had any false notions as to the general character of the heart's electrical field or that they considered their method of determining the position of the electrical axis of the heart entirely free of error. In 1921, a paper by Lewis, Drury, and Iliescu[2] on the electrical axis of the auricle in clinical cases of auricular flutter raised a question as to the conditions under which the principles of Einthoven's triangle are applicable. A letter to Einthoven concerning this matter was answered by him on Nov. 21, 1921, as follows:

"In regard to the equilateral triangle I fully agree with you. I assumed in my original paper 'Ueber die Richtung und die Manifeste Grösse der Potentialschwankungen etc.,' in the center of the triangle a 'bipole,' that is to say two points lying very close together and showing a potential difference. The triangle was supposed to be a homogeneous sheet of conducting material and in regard to the distance between the two points of the bipole, of a large, let us say infinite extent.

"The applicability of this scheme to the ordinary leads of the human body depends indeed on the fact that the electrodes are at a relatively great distance from the heart. If they are placed near the heart the errors are greater and the more so the closer they get to the heart. Even in the case of the ordinary leads from the limbs the results cannot be absolutely exact."

A number of attempts have been made to test the validity of Einthoven's triangle by impressing a constant or variable voltage upon two metallic electrodes thrust into the heart of a cadaver and comparing the position of the electrical axis, computed by Einthoven's method from the potential differences recorded in the standard limb leads, with the direction of the impressed potential difference. The first experiment of this kind was performed by Fahr and Weber.[3] The heart was exposed and two small zinc needles were thrust into its

wall, one in the region of the sinus node and the other at the apex. When 1/5 volt was applied to these electrodes the deflection in Lead I was 10 mm., that in Lead II was 46 mm., and that in Lead III was 36 millimeters. The angle between the line defined by the two electrodes and the direction defined by Lead I was estimated at 75 degrees. The corresponding angle computed from the deflections in the three leads was approximately 3 degrees larger.

A similar experiment was performed by Wagner[4] on the cadaver of an infant who had died eight days after birth. In this instance two zinc needles were thrust through the precordial tissues into the heart and a potential difference of approximately 6 volts was impressed upon them. Three milliammeters were used to measure the resulting potential differences between the extremities. In the first test the currents in Leads I, II, and III were 6, 10, and 4 ma., respectively; when the input voltage was increased, these currents rose to 8, 13, and 5 ma., respectively. The chest was then opened, and it was found that one of the needles had entered the heart near its base, and the other entered just above the apex. The currents in the three leads were the same after opening the chest as before. When the electrodes were replaced so that the line defined by them made an angle of approximately 60 degrees with the direction of Lead I the currents in the three leads were 3, 6, and 3 ma., respectively. When the electrodes were arranged so that the line defined by them made an angle with the frontal plane, the currents in the standard leads were 3, 5, and 2 ma. when the projection of this line on the frontal plane was parallel to Lead II, and 4, 2, and −2 ma., respectively, when it was parallel to Lead I. This experiment and a large number of experiments on models of various types led Wagner to conclude (contra Groedel and Straub) that the theory of the equilateral triangle was in all respects well founded.

On March 1, 1934, Johnston, Kossmann, and Wilson[5] performed an experiment on the cadaver of a man who had died of carcinoma of the face complicated by pneumonia more than a week before. During the interim, the cadaver had been stored in the morgue in the supine posture, and it was suspected that in addition to pronounced post-mortem changes there had been some gravitation of the body fluids into the more dorsal tissues. The input electrodes consisted of two small brass rods, insulated except at the sharpened tips and fixed in a wooden frame. The frame permitted the rods to be moved endwise so that when they were thrust into the precordium the depth of the tip of each rod was independently adjustable. By means of a rotating contact breaker a potential difference of approximately 18 volts was rhythmically impressed upon these electrodes after they were in place. The thickness of the chest, measured from precordium to back, was 21 centimeters. The electrodes were first thrust through the chest wall in the third intercostal space, one just to the right and the other just to the left of the sternum. The depth of the tip of the former (the negative electrode) was 5.7 cm. and that of the tip of the latter (the positive electrode) was 8.8 centimeters. The deflections recorded in Leads I, II, and III measured 26, 12.75, and —13 mm., respectively. Moving the left leg electrode to the pubis had no appreciable effect. Increasing the depth of the positive elec-

trode to 10 cm. and decreasing the depth of the negative electrode to 5 cm. produced only very minor changes in the potentials of the three extremities, measured with respect to that of a central terminal connected to these electrodes and also to an electrode in the left interscapular region through resistances of 10,000 ohms. This procedure increased the positivity of the electrode on the back from 2 to 4.5 tenths millivolt.

When the positive electrode was in the third intercostal space near the left sternal edge with its tip 10.7 cm. below the skin, and the negative electrode in the fourth intercostal space and on the same vertical line but with its tip 5.5 cm. below the skin, the deflections in Leads I, II, and III measured 1.5, —30.5, and —32 mm., respectively. In this case, however, increasing the depth of the positive electrode to 15 cm. increased the deflection in Lead I to 12 and that in Lead III to —35 mm. and reduced the deflection in Lead II to —23 millimeters. The factor responsible for this unexpected result was not discovered.

These cadaver experiments by different workers support Einthoven's belief that when a potential difference is generated between two points lying within or close to the heart, the deflections in the three standard limb leads are very nearly proportional to the cosines of the angles made by the frontal projection of the axis of this potential difference with the corresponding sides of his equilateral triangle. It is, of course, true that the conductivity of dead tissues is by no means the same as the conductivity of living tissues. If experiments of the kind described could be performed on living subjects would the results be vastly different? In 1920, Wilson and Herrmann[6] made a crude test of the validity of Einthoven's triangle in the course of some experiments on dogs in which the heart was stimulated rhythmically for the purpose of studying its refractory period. The stimulus was the current delivered by the secondary coil of an inductorium when the circuit through the primary coil was broken. Sharp deflections representing the induction shocks were observed in the limb leads. A stimulating electrode was then attached to each terminal of the secondary coil and the two electrodes were thrust into the ventral wall of the heart, one near the base and the other near the apex, in such a way that the line joining them was nearly parallel to the long axis of the body. The deflections produced by the induction shocks in the limb leads measured 2, 16, and 14 mm., respectively, under these circumstances. When the electrodes were so placed that the line joining them was perpendicular to the long axis of the body, these deflections measured 9, 3, and —6 mm., respectively. Except for the response to those shocks which fell outside the refractory period, the heart continued to beat normally. Its ventral surface was exposed and the lungs were not fully inflated. We doubt that the string galvanometer was capable of recording the very brief induction shocks with great accuracy. Nevertheless, it will be noted that the direction and relative size of the deflections in the limb leads were about what would be expected on the basis of the principles of the equilateral triangle.

It is clear that Einthoven regarded the electrical field associated with the heartbeat, in so far as it is represented by the potential differences recorded by the standard limb leads, as approximately equivalent at any given instant to

that of a dipole or doublet located in a homogeneous isotropic medium of large extent. In all probability this view was suggested by a well-known theorem on the potential of a complex of electric charges distributed in a dielectric and enclosed by a spherical surface of the smallest adequate radius. The potential of such a complex at any point outside this surface may be expressed in the form of an infinite series of spherical harmonics. When the net charge of the complex is zero, the successive terms of the series represent the potential of a dipole, the potential of a quadrapole, the potential of an octupole, and the potentials of multipoles of increasingly higher order.[7] At points sufficiently distant from the center of the sphere the field may legitimately be regarded as closely approaching that defined by the first term alone, in other words, that of a dipole.[7]

Between the electrical field of a complex of charges of the kind described and the electrical field associated with the heartbeat, there is an obvious analogy. The sources and sinks of the heart's field corresponding to the positive and negative charges of the complex all lie within a circumscribed region: the smallest sphere in which the heart can be enclosed. The action current which flows out of any given cardiac fiber re-enters the same fiber in a neighboring region. Each source is, therefore, associated with a sink of equal strength, and it is clear that the cardiac field is not only comparable to that of a distribution in which the net charge is zero, but to a complex consisting of doublets only. Between an electrostatic field and the cardiac field there are, however, some obvious differences. In the first place, the latter, unlike the former, varies with the time. Nevertheless, the cardiac field at any given instant has always been treated as if it were stationary; the effects of induction have been neglected. The justification for this procedure lies in the low frequency of the cardiac currents, the relatively small size of the conductor involved, and the relatively small conductivity of the body tissues, and also in the results of experiments of the kind we have already described in which the distribution of variable currents of low frequency has been studied. In the second place, the heart is imbedded in a medium which is neither strictly homogeneous and isotropic nor infinite in extent. The effect of the requirements imposed by the boundary conditions involved is to superimpose upon the field of the cardiac sources and sinks, as it would exist in free space, the field of a layer of doublets at the body surface[8] and the fields that would be produced by the presence of a single layer of charge on every surface separating tissues of unlike conductivity. The double layer is required to annul the field of the cardiac sources and sinks outside the body and each of the single layers to make the product of the conductivity and the electric intensity normal to the boundary surface the same on both sides of it. The effect of the double layer will, in general, be greatest at the body surface and least at points most distant from it; the effect of each single layer will be greatest near the surface on which it lies. It is, of course, out of the question to compute the exact effect of the boundary conditions that must be met in the case of conductors like the body which are irregular in shape and complicated as regards the arrangement and electrical properties of their constituent parts. It is possible, however, to compute the field of a centric or eccentric doublet in a sphere made up of spherical

shells of specified conductivities. On the basis of such computations, of the available experimental knowledge of the specific conductivities of the body tissues, and of the results of experiments of the kind described in previous paragraphs it seems to us that Einthoven's views as to the nature of the heart's electrical field, in so far as they are expressed in, or may be inferred from, his published work, are still in accord with all the known facts.

UNIPOLAR LEADS

In 1932, Wilson, Macleod, and Barker[9] described a new type of electrocardiographic leads in which a central terminal connected through equal resistances to electrodes on the right arm, left arm, and left leg is paired with an exploring electrode placed on the precordium or upon any other part of the body. They held that leads of this kind are essentially unipolar in the sense that they record the potential variations of the exploring electrode with respect to a reference point which remains at very nearly the same potential throughout the cardiac cycle. It was shown that the sum of the differences in potential between any number of electrodes and a nodal point connected to these electrodes through equal resistances must be zero as a consequence of Kirchhoff's first law. The potential of the central terminal is consequently equal at every instant to the mean of the potentials of the electrodes on the extremities. On the basis of the assumptions upon which the equilateral triangle of Einthoven, Fahr, and de Waart is based plus the additional assumption that electrical forces of cardiac origin which are perpendicular to the plane of the standard limb leads have no significant effect upon the potential variations of the extremities, it was also shown that the potential of a central terminal connected through equal resistances to electrodes on the right arm, left arm, and left leg is not materially affected by the heartbeat and may be considered nearly constant throughout the cardiac cycle.

This conclusion promises to become the subject of a controversial discussion no different in character and not less lengthy than the one that has revolved around Einthoven's triangle. Several kinds of experiments bearing on its validity have been reported. Burger and Wuhrmann[10] mention that one of them compared the potential of the central terminal of Einthoven's triangle with that of other central terminals each connected to three electrodes equidistant from the heart and lying at the apices of a triangle enclosing it. No details are given, but it is stated that the differences in potential between the various terminals were negligibly small. Arrighi[11] is known to have carried out experiments of a similar kind. So far as we know his work has not yet been published, but all of his experiments that we have knowledge of yielded results comparable to those reported by Burger and Wuhrmann. We have performed one experiment of the same kind and the results of such experiments are predictable on the basis of Arrighi's published work. In his doctoral thesis[12] he described his experience with three leads which formed the sides of a sagittal triangle that enclosed the heart. One electrode was placed in the left submaxillary region close to the chin, the second 3 or 4 cm. to the left of the midpoint of a line joining the umbilicus with the center of the pubis, and a third in the left interscapular space, approximately at

the level of the spinous process of the seventh thoracic vertebra. In almost all of the more than fifty cases of various types that were studied, it was found that the voltage of the deflection recorded at a given instant in the cardiac cycle by leading from the electrode on the jaw to that on the abdomen was very nearly equal to the sum of the simultaneous voltages recorded in Leads II and III divided by the square root of 3. It is not difficult to demonstrate algebraically that whenever this is the case the difference in potential between a central terminal connected to the usual extremity electrodes and a central terminal connected to Arrighi's submaxillary and abdominal electrodes only cannot be appreciably greater than that between his abdominal electrode and the left leg electrode. Since these two electrodes are similarly situated with reference to the heart we may expect that they will always be at nearly the same potential. A lead from the central terminal of Einthoven's triangle to a central terminal connected to all three of Arrighi's electrodes will, therefore, ordinarily yield deflections similar to, but approximately one-third as large as, those obtained by leading from the first of these terminals to the electrode on the back.

The tracings obtained in the only experiment of this kind that we have carried out are reproduced in Fig. 1. In addition to the standard and the unipolar limb leads (taken by Goldberger's method) the following special leads (taken with the electrocardiograph at twice the normal sensitivity) are shown: (1) a lead from the central terminal of the Einthoven triangle to a terminal connected to all three of the Arrighi electrodes; (2) the same lead after the electrode on the back had been disconnected from the second terminal; (3) the same lead after reconnecting the electrode on the back and disconnecting the electrode on the jaw; (4, 5, and 6) leads from the central terminal of the Einthoven triangle to each of the three Arrighi electrodes in turn; (7) a lead from the same terminal to one connected through equal resistances to two electrodes, one on the left back near the base of the neck and the other just to the left of the sacrum; (8 and 9) leads from the same terminal to each of these electrodes in turn. It will be noted that the greatest potential difference between the central terminal of the Einthoven triangle and that of the Arrighi triangle did not exceed 0.15 mv and that the first of these terminals was negative with respect to the other. It should also be noted that the deflections of Lead $V_{T'} - V_T$ are similar to those of Lead $V_B - V_T$ but about one-third as large.

In the case of normal subjects, an electrode placed on the back directly behind the heart is ordinarily positive with respect to the central terminal of the Einthoven triangle throughout the greater part of the QRS interval. For the time being we may assume, therefore, that this terminal is normally slightly negative and that of the Arrighi triangle slightly positive when the sagittal component of the heart's electromotive force has an anteroposterior direction. By connecting these two terminals together or by connecting an electrode on the back to the central terminal of Einthoven's triangle we might perhaps obtain a reference point more nearly indifferent than either.

Several investigators have attempted to ascertain the magnitude of the potential variations of the central terminal of Einthoven's triangle by means of

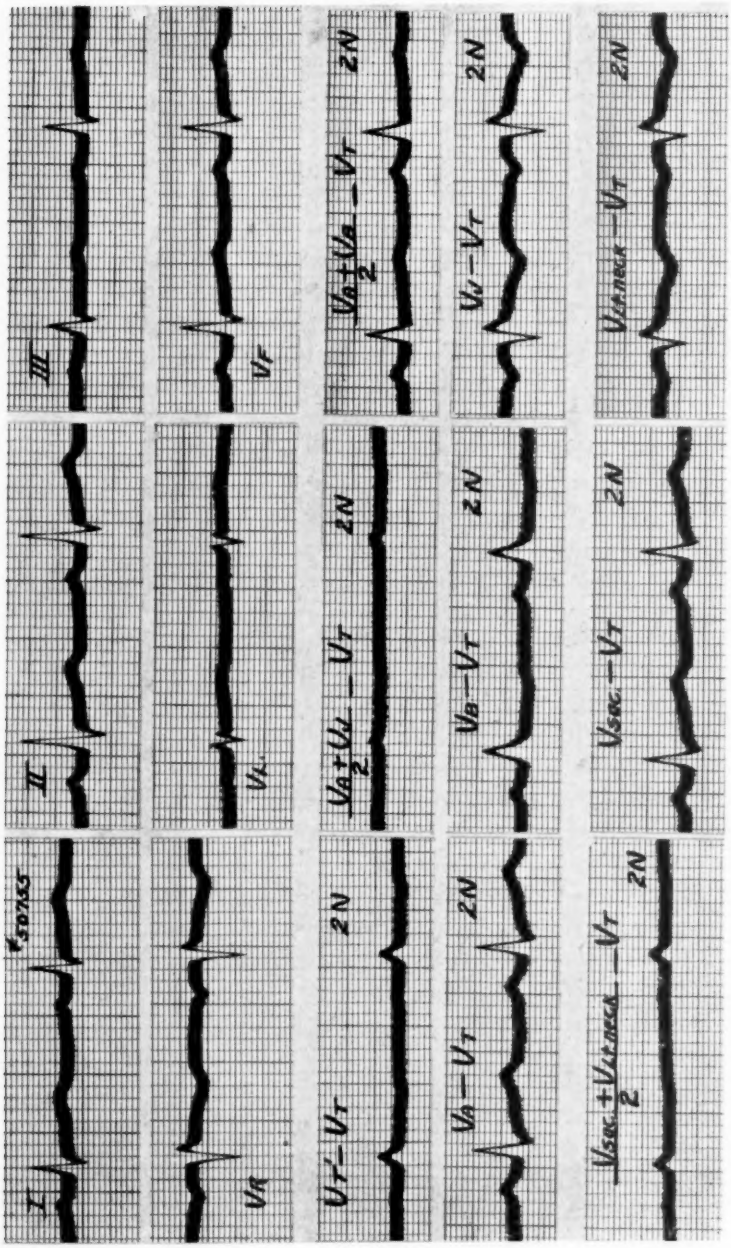

Fig. 1.—Comparison of the central terminal of the Einthoven triangle with that of the Arrighi triangle. A deflection of 2 cm. represents a voltage of 1 millivolt.

immersion experiments. Eckey and Fröhlich[13] placed their subjects in a large wooden tub lined with metal and filled with distilled water; contact between the subject and the metal lining was prevented by a suitable wooden support. The surface of the water was screened by a sheet of metal placed beneath it and in contact with the metal lining of the tub. The subject breathed through a glass tube brought out through a small hole in this metal lid; other small openings accommodated the electrocardiographic cables. The electrodes employed were not insulated. It was found that immersion of the subject in distilled water did not materially reduce the size of the deflections in the standard limb leads and that the cardiac field did not extend to the water outside the metal screen. The largest potential variations of the central terminal with respect to this screen were of the order of 0.2 to 0.3 mv in all of the unspecified number of experiments performed.

Burger[14] employed a tub lined with zinc and filled with tap water, and he did not immerse the face of his subjects. He insulated his electrodes from the bath with rubber sheeting. Immersion reduced the deflections of the standard limb leads to approximately 75 per cent of their original size. In five experiments on normal subjects the voltage of the largest deflection obtained by leading from the metal screen to the central terminal was about 0.26 millivolts. In four of the five cases the central terminal was slightly negative with respect to the zinc shield during the greater part of the QRS interval.

We have performed one immersion experiment of a somewhat different kind. After the standard limb leads had been taken, the subject was immersed up to the chin in a small fresh-water lake. The short-circuiting effect of the water reduced the size of the deflections in these leads to approximately one-half their original size (Fig. 2). There was also a slight change in the form of the ventricular complexes, probably because, when in the water, the subject was not able to assume exactly the posture in which the control curves were taken. The potential variations of the limb electrodes and the central terminal with respect to a large metal electrode suspended in the lake at a distance of about 11 feet from the body were recorded with an amplifier-type electrocardiograph at twice its normal sensistivity. The largest potential variation of the central terminal measured 0.15 mv; it was negative to the reference electrode (Fig. 3). The distant and the left leg electrode remained at practically the same potential throughout the cardiac cycle; we assume that in a series of experiments this would happen only rarely. Both arms and a point on the right scapula were negative with respect to the distant electrode during the greater part of the QRS interval.

Burger was uncertain as to whether the magnitude of the potential variations of the central terminal could be ascertained by the method which he employed for this purpose. Wolferth and Livezey[15] have expressed the opinion that "the reason advanced by Eckey and Fröhlich to support the claim that their immersion procedure can be used to obtain unipolar leads has no merit." The lack of agreement exemplified by this comment is basically similar in origin to the controversy between the proponents of the "negativity hypothesis" and the proponents of the "doublet hypothesis" which began some ten years ago. As the

years have passed it has become more and more apparent that the chief sources of this controversy are differences in point of view, in opinion as to the proper choice of a reference point for the measurement of bio-electric fields, and in the sense in which the word "potential" is employed between those who are mainly interested in the action currents of isolated nerves bounded by a dielectric and those who are mainly concerned with the action currents of the heart which is imbedded in a conducting medium.* Because many who do not understand the nature of the dispute have become uncertain as to whether unipolar precordial and unipolar limb leads are desirable and as to whether they are theoretically or practically possible, we have re-examined and attempted to clarify the ideas upon which the concept of an indifferent electrode is founded.

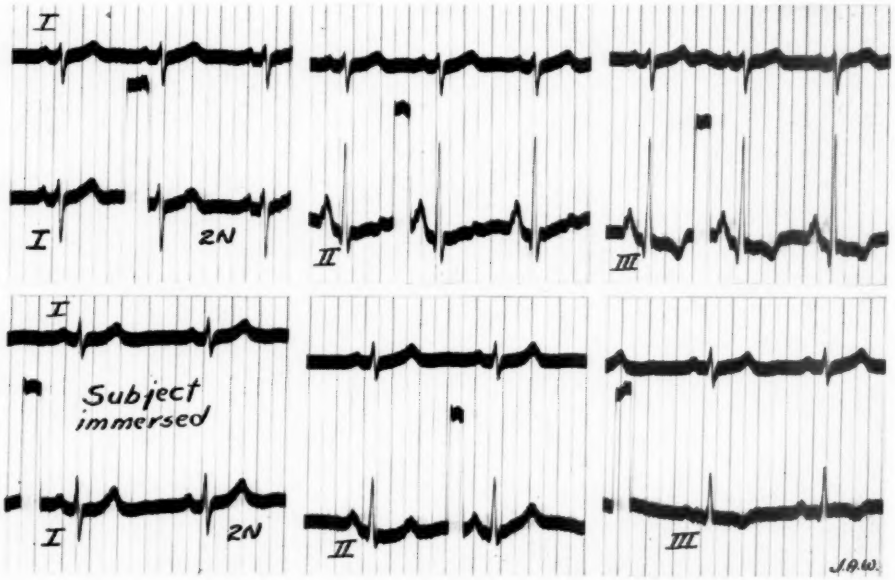

Fig. 2.—Electrocardiograms of a normal subject taken with the electrocardiograph at twice the normal sensitivity (2 cm. equals 1 mv).

The sequence of events and the considerations which led to the introduction of the central terminal for the purpose of obtaining unipolar leads are in outline quite simple. In 1916, Lewis and Rothschild[17] had difficulty in recognizing the "intrinsic" deflection in leads in which paired contacts were placed on the exposed ventricular surface. They attributed this difficulty to the arrival of the impulse beneath both electrodes almost simultaneously. To avoid it they left one electrode in place and moved the other, sometimes to another part of the heart's surface, and sometimes to the chest wall. They found the last procedure par-

*The champions of the "negativity hypothesis" focus their attention upon the action potential, or time-course of the voltage across the cell membrane during excitation and therefore choose an injured region which is incapable of responding to the excitatory process as their reference point. (For a discussion of such leads see Col and Curtis.[16]) Cardiologists who are forced to deal with the distribution of the cardiac action currents in a volume conductor are confronted by problems of an entirely different sort. They cannot apply the same principles to the interpretation of their tracings, must use the term "potential" in a different sense, and, consequently, must find another point of reference more useful for their purposes.

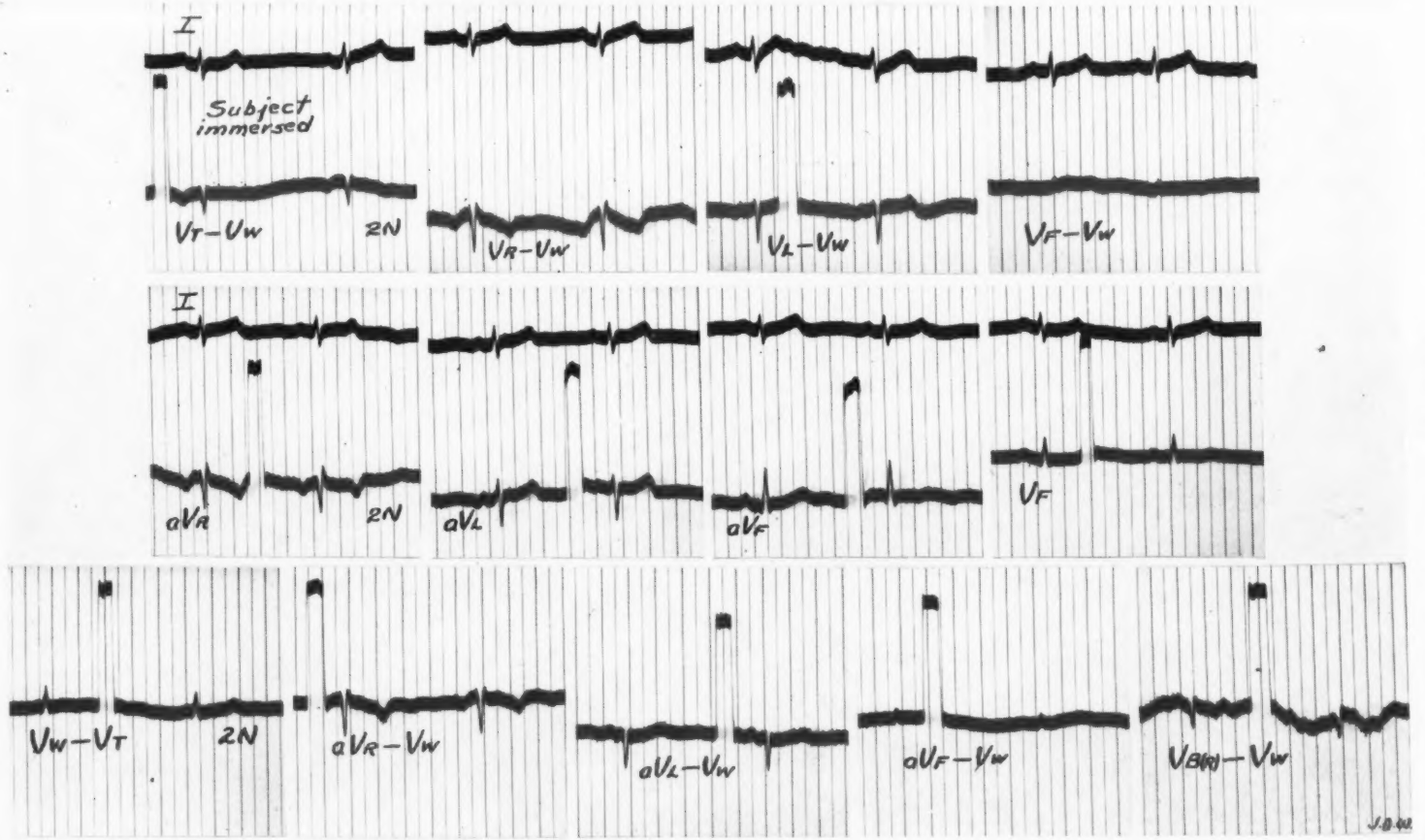

Fig. 3.—Records showing the potential variations of the central terminal and of electrodes on the extremities with reference to an electrode 11 feet from the subject. These tracings were taken with the electrocardiograph at twice the normal sensitivity. The symbols used have the following significance: V_R, V_L, and V_F represent the potentials of the electrodes on the right arm, left arm, and left eg, respectively, when connected to the central terminal through resistances of 5,000 ohms; aV_R, aV_L, and aV_F represent the potentials of these same electrodes when disconnected from the central terminal; V_T is the potential of the central terminal; V_W is the potential of the distant reference electrode; and $V_{B(R)}$ is the potential of an electrode on the right scapula. Leads from an extremity electrode to the central terminal are labelled V_R, etc., or aV_R, etc., in the usual way.

ticularly serviceable, and they clearly regarded the chest contact as without influence upon the position of the intrinsic deflection in the QRS interval. It is not certain that they considered this contact as indifferent in other respects; or that they believed the potential variations of this contact too small to have any significant influence upon the form of the tracings they obtained. In this laboratory the electrocardiograph is employed at one-twentieth of its normal sensitivity when leads of the kind in question are taken. So long as the distant contact is not placed close to the heart, its location can, therefore, have no important effect upon the size or form of the deflections recorded. On the other hand, moving the direct contact from one part of the heart's surface to another is almost certain to give the resulting curve an entirely different character. If we think of the cardiac field in terms of the current density, it is obvious that it is very intense in the vicinity of the epicardial surface, and, in comparison, of negligible strength in the neighborhood of the distant electrode. In the former region, the variations in the intensity of the field during the cardiac cycle are very large; in the latter they are very small. It is logical, therefore, when employing leads of this sort, to regard the potential variations recorded as characteristic of the region upon which the direct contact rests and to think of the distant electrode as indifferent and without influence upon the form of the curve; in other words, to consider leads of this kind unipolar.

In 1920, Wilson and Herrmann[18] performed the following experiment. A line was drawn from the fourth left costal cartilage to a point on the left leg just below Poupart's ligament. A small electrode (A) was placed at the upper end of this line and similar electrodes (B, C, D, and E) were spaced along its course at points 5, 10, 15, and 20 inches, respectively, below the first. With the electrocardiograph at half the normal sensitivity, Leads A-B, B-C, C-D, and D-E were then taken. The largest QRS deflection measured 20 mm. in the first, about 3 mm. in the second, and about 1 mm. in the third of these leads. No deflection of any kind was visible in the fourth. The results of this experiment suggested that, if an electrode on the central part of the precordium were paired with a contact at a considerable distance from the heart, the form and size of the ventricular deflections obtained would be nearly the same regardless of whether the second electrode were above, below, to the right of, to the left of, or behind this organ. The experiment was tried and this conclusion was confirmed.[19] Theoretical considerations and the resemblance in general contour between the ventricular complexes of leads in which a precordial electrode was paired with a contact far from the heart and those which Lewis and Rothschild obtained by leading from the epicardial surface of the exposed ventricles to some point on the chest wall led to the belief that leads of this kind are actually semidirect leads from the anterior ventricular surface, and this conclusion was published by Wilson, Wishart, and Herrmann[20] in 1926. A preliminary report of experimental and clinical observations bearing upon the value of such leads for the purpose of differentiating left from right bundle branch block was published in 1930 by Macleod, Wilson, and Barker.[21] The publication of the complete account[22] of these observations was postponed until the components of the human pre-

cordial curves which could legitimately be ascribed to potential variations of the distant electrode,[22] which had been placed on the left leg, could be computed and eliminated. The central terminal was introduced[9] with the object of accomplishing the same purpose more directly by reducing the potential variations of the reference contact to a minimum. This seemed desirable in order to make precordial leads of the kind in question as nearly unipolar, and therefore as nearly comparable to direct leads of the sort used by Lewis and Rothschild, as might be possible.

The central terminal is founded upon the idea that, so far as the limb leads are concerned, the electrical field of the heart is approximately equivalent to that of a dipole lying in or near the plane of these leads and that the principles upon which Einthoven's equilateral triangle is based are sound. If this view is tenable the potential of this terminal should remain at nearly the same level throughout the cardiac cycle. It is true that the sum of the potentials at the apices of an equilateral triangle enclosing a centric dipole which varies in strength will not remain constant unless the plane which passes through the dipole and is perpendicular to its axis separates the conducting medium involved into two identical parts. It is also true that the body is not symmetric with respect to any plane that passes through the heart. On the other hand, the magnitude of the effects produced by a lack of symmetry with respect to any such plane must decrease as the distances from the heart to the boundaries responsible for it increase. It was shown, for example, by Wilson[19] that when a coil of copper wire is placed in the field generated in a layer of electrolyte by a centric source and sink close together, the resulting modification of the field increases as the disturbing factor is brought closer to the region where the current density is maximal.

With respect to immersion experiments and the like, it is evident that factors which increase the asymmetry of the conducting medium surrounding the hypothetical cardiac dipole will tend to increase, and factors that have the opposite effect to decrease the potential variations of the central terminal with reference to a point that is completely indifferent. Placing the body in a lake or in a smaller body of water bounded by a metal screen, cannot change the location of the boundaries which define differences in tissue conductivity and it is hardly possible that it can significantly increase the flow of current across them. It does alter the heart's field by modifying the conditions at the body surface. The short-circuiting effect of the conducting fluid naturally reduces the potential differences between the various parts of this surface including those between one extremity and another and between the extremity electrodes and the central terminal. The magnitude of this effect is proportional to the conductivity of the water in which the body is immersed. The conductivity of distilled water is of the order of 2×10^{-4} mhos per meter and that of lake water and tap water is five to fifty times as great.[7] If the potential variations of the three extremity electrodes are reduced proportionately and in the same measure as the differences in potential between them, the potential variations of the central terminal will be diminished in the same degree.

Even when it has comparatively little effect upon the size of the deflections in the limb leads, as in the experiments of Eckey and Fröhlich, or reduces the size of all these deflections in the same proportion, as in those of Burger, immersion of the body will not have the same effect upon the potential variations of all three extremity electrodes if it brings about differences in their spatial relations with respect to the new bounding surfaces. In experiments of the kind performed by the investigators just mentioned, a contact or near-contact between one of these electrodes and the shielding metal screen would bring both to the same or nearly the same potential. The difference in potential between the screen and the central terminal would then become equal or nearly equal to the difference in potential between the latter and the extremity electrode concerned. In other words, the effect of the asymmetric arrangement of the electrodes would be to make the potential variations of the central terminal with respect to the screen larger rather than smaller.

Whether bringing one of the extremity electrodes very close to the screen would alter the potential of the former, that of the latter, or that of both depends upon what is considered the proper reference point for the measurement of the potential of the cardiac field. By connecting the electrode or the screen to earth the absolute potential of either could be maintained at zero. Since the conductivity of metal is roughly fifty billion times that of distilled water, the intensity of the electric forces produced by the heart must be infinitesimal outside the metal shield, and we agree with Eckey and Fröhlich that the potential of the screen should be considered completely indifferent with respect to the cardiac field.

Differences of opinion on questions of this kind have led to much confusion. Their source lies in the circumstance that the absolute potential of a given point on an isolated conductor in which electric currents are flowing is indeterminate unless the total charge on the conductor is known or the potential of one of its points has been fixed by grounding it. This difficulty arises because an isolated conductor may carry a static charge of unknown magnitude. Such a charge over its surface will raise or lower the absolute potential by the same amount at every point of the conductor but will have no effect upon the currents flowing through it. In the case of an infinite conductor this situation cannot arise. If the conductivity of the isolated conductor under consideration is large enough, we may think of it as in contact over its whole surface with an infinite conducting medium possessing a very much smaller conductivity and thus make it possible, at least theoretically, to choose infinity as our reference point for the measurement of the field.

The electrical field associated with the heartbeat presents some additional complications because it varies with time. We have been treating it as though, at any given instant, it had the same characteristics that it would have if it were not changing. Let us suppose, therefore, that there is a static charge on the body (or any conductor of which it is a part) which varies in magnitude from instant to instant, and that the inductive effects of this varying charge may be neglected. The potential variations produced by it will then be of the same magnitude at every point of the conductor and will have no effect upon the cardiac currents.

Potential variations of this sort are imposed upon the cardiac field by selecting some arbitrary point on the body and grounding it, or what amounts in effect to the same thing, making it the reference point for the measurement of the potential. It is obvious that if the potential of any chosen point was not constant before, and is constant after it has been grounded, this procedure must either impose upon every other point of the conductor variations in potential of the same absolute magnitude as those abolished, or alter the distribution of the cardiac currents. Connecting the body to earth does not have an effect of the latter kind* large enough to be detected by the electrocardiograph.

If one investigator places his reference electrode on a freshly injured spot on the ventricular surface and connects it to earth, he will arrive at the conclusion that all ventricular complexes represent a combination of two monophasic responses. Another who places his reference electrode on an uninjured part of the ventricular surface will not find this view attractive. In leads from all parts of the body surface each will record large complexes that are practically identical in form, and both will disagree with a third investigator who has placed his reference electrode as far from the heart as possible and believes that the magnitude of the potential variations produced by the heartbeat diminishes rapidly as the distance from the heart increases. As to the variations in the difference in potential between two specified points on the body surface, all will come to the same conclusion only if they compare them directly by leading from one to the other, for neither of the first two investigators will be able to estimate these potential differences by comparing leads from each of the two points to his reference electrode unless he makes use of a measuring machine. It is clear that the arbitrary choice of a reference point for the measurement of the cardiac field in terms of the potential, and also a purely empirical approach to the selection of the most useful bipolar leads, is likely to yield a harvest of confusion rather than enlightenment. We can, of course, give up the concept of the potential and think of the field of the heart in its vector form; that is to say, as a distribution of electric currents. Unfortunately, vector fields, in which three numbers must be associated with every point, are much more difficult to visualize and to analyze than scalar fields.

Three-dimensional fields of any kind, vector or scalar, are difficult to visualize unless they have some degree of symmetry. In the case of a field that has this property, it is profitable to fix the attention upon the point, line, or plane with respect to which the symmetry subsists. There is nothing to be gained by choosing a reference point for the measurement of the potential in such a way as to give the measured cardiac field a less symmetrical aspect than that which it has when expressed as a system of current lines and isopotential surfaces. If this is to be avoided the potential of the reference electrode should be the same as that of the point or points with respect to which the cardiac field is most nearly symmetrical;

*It would seem that in this case the fluctuating charge on the body is represented by a flow of charge into and out of a condenser of which the plates are the body and the earth. Both the capacity of this condenser and the resistance in series with it are small, so that the time constant of the circuit involved must be very short, and the static charge involved very small. There is no chance that the redistribution of the amount of electricity required to change the potential of the body with reference to the earth by a few millivolts could be detected by any instrument used to take electrocardiograms.

better still, if it were possible, the same as that of points far enough from the heart to be beyond an appreciable influence of this field. In the latter case the potential would be zero where the intensity of the field was negligible. The potential of the central terminal is the mean of the potentials of the apices of Einthoven's triangle and these are nearly as far from the heart as any other points on the trunk. If the field of the heart, so far as its least intense parts are concerned, may be regarded as nearly equivalent to that of a dipole located within the heart, the potential of this terminal is also that of the center of the dipole, the point about which the cardiac field is most nearly symmetric, provided that the electric forces perpendicular to the plane of the limb leads have no significant effect upon the mean potential of the extremities.

If the potential variations of the reference electrode are large, the ventricular complexes of all leads from regions where the cardiac field is considerably weaker and therefore varies less will be very much alike in form. The occurrence of strikingly similar complexes in leads from points that are widely distributed over the body and differ greatly in respect to distance and direction from the heart is a clear indication that the reference electrode is far from indifferent. If the cardiac field at points far from the heart is nearly equivalent to that of a doublet, leads from two points equidistant from this organ and at opposite ends of a line which passes through its center should yield complexes exactly opposite in character if the leads employed are unipolar. The average potential over a spherical surface, due to charges within it, is zero if the net charge is zero[24] as in the case of dipoles. It seems probable, therefore, that the average of the *cardiac potential** over the body surface must have a small value. If the reference electrode is indifferent and complexes of one kind are obtained from all parts of a region close to the heart, such as the precordium, complexes of the opposite type should be obtained from a still larger diametrically opposite region, such as the back, which is farther away from the heart. So far as we are able to judge from our experience with the central terminal, its potential is ordinarily close to the average of that of the body surface.

In concluding this discussion we may emphasize the fact that all of the available data which have a bearing upon the questions at issue are consistent. This is a very important consideration in estimating their significance. The cadaver experiments indicate that in spite of the irregular shape of the body and the somewhat eccentric position of the heart it is possible to ascertain the orientation of the frontal projection of the heart's electrical axis with considerable accuracy by Einthoven's method. All the immersion experiments that have been carried out gave substantially the same results. In the case of normal subjects the potential of the central terminal with respect to an electrode which bore essentially the same relation to all or nearly all parts of the body surface was slightly negative throughout the greater part of the QRS interval and did not vary through a range of more than 0.3 millivolts. The chief question that arises in connection with these experiments concerns the relative magnitude of the potential variations of the central terminal before immersion with respect to its potential

*We use this term to indicate the potential of the cardiac sources and sinks under the boundary conditions imposed upon the field to which they give rise.

variations after immersion. Due allowance has been made for the short-circuiting effect of the water on the basis previously indicated. That other factors, such as large variations in skin resistance from point to point, which might alter the magnitude of the potential variations in question when the subject was immersed could have had substantially the same effect in all the experiments performed seems very improbable. The observations on the difference in potential between the central terminal of the Einthoven triangle and that of the Arrighi triangle suggests that that the small negative potential of the former observed in the immersion experiments was due to the effect of electric forces having an anteroposterior direction. It is desirable to know the magnitude of the error involved in determining the inclination of the sagittal projection of the heart's electrical axis by Arrighi's method. This organ is closer to the anterior wall of the chest than to any other part of the body surface and its position with respect to his triangle is not precisely the same as its position with respect to the triangle of Einthoven.

THE INTERPRETATION OF THE PRECORDIAL ELECTROCARDIOGRAM

A comprehensive article[25] on this subject has recently been published from this laboratory. We propose here to supplement and not to repeat what was said in that article. We shall confine our remarks to a few examples of types of precordial electrocardiograms that have not been adequately discussed.

Incomplete Right Bundle Branch Block.—The electrocardiogram reproduced in Fig. 4 is that of an obese boy, aged 9 years, who had a speech defect and displayed evidence of general hypoplasia and mental retardation. The heart was not enlarged, no significant murmurs were heard, and the blood pressure was 96/40. There was no history of cyanosis at birth and none was present at the time of the examination. The limb leads show rather pronounced left axis deviation, a QRS interval which measures approximately 0.09 second, and both an R and an R′ wave in Lead III. Double R waves are also present in precordial leads V_1, V_2, and V_E. We believe that many precordial electrocardiograms of this kind represent incomplete right bundle branch block. We have encountered them frequently in all types of heart disease and also in many instances in which there was no other evidence of heart disease. Our interpretation of these curves is based on the occurrence of ventricular complexes of the same form in an electrocardiogram which was discussed in the article previously referred to (see Figs. 14 and 15 of that paper[25]). In that instance they alternated with complexes characteristic of complete right branch block, and the initial phases of the two types of complexes were identical in all leads. The difficulty is that one often sees an embryonic secondary R, that is to say, a conspicuous notch on the ascending limb of S, or a small terminal R′ deflection in Lead V_1 in cases in which there is not only no other evidence of heart disease but no increase in the QRS interval and no trace of a similar deflection in Lead V_2 or Lead V_E. The diagnosis of incomplete right bundle branch block must, therefore, be made with caution. We think that this diagnosis is more likely to be correct when the secondary R

wave is conspicuous and is present in Lead V_E as well as in Lead V_1 and the QRS interval measures at least 0.10 second in the limb leads. This diagnosis should not be made unless the R′ deflection rapidly decreases in size as the exploring electrode is moved toward the left side of the precordium as it invariably does in complete right branch block. In some cases Lead V_1 displays an unusually prominent R deflection with a prominent notch or slur on its ascending limb, and if the exploring electrode is moved farther to the right a broad bifid R or a final R′ deflection is recorded. This situation is illustrated in Fig. 5, in which is reproduced the electrocardiogram of a boy, aged 17 years, who had a very loud, rasping

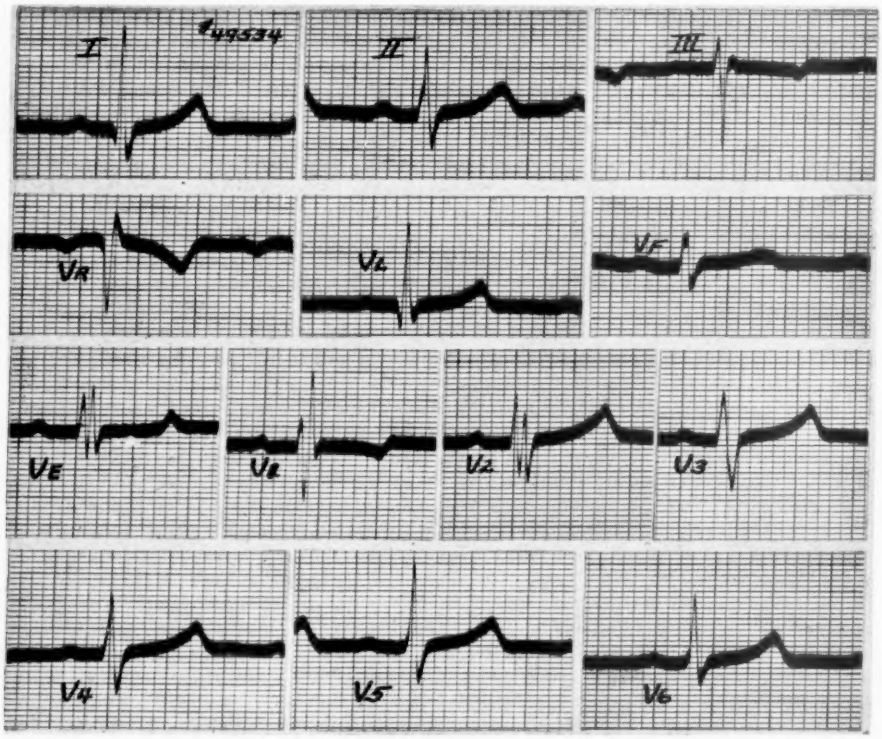

Fig. 4.—Incomplete right bundle branch block.

systolic murmur accompanied by a thrill in the pulmonic area. He was not blue at birth but a cardiac abnormality was noted a year later. There was no cyanosis and roentgenographic examination of the heart was negative. The position of the electrical axis, the small size of the R wave in Lead V_6 and in the leads from the left back (V_7 and V_8), and its large size in the leads from the right side of the precordium suggest right ventricular hypertrophy. However, this abnormality, which was suspected on clinical grounds also, does not satisfactorily explain the occurrence of secondary R waves in the leads from the right side of the chest.

Occasionally, we have seen precordial electrocardiograms which had all the characteristics of those that are diagnostic of complete right bundle branch block

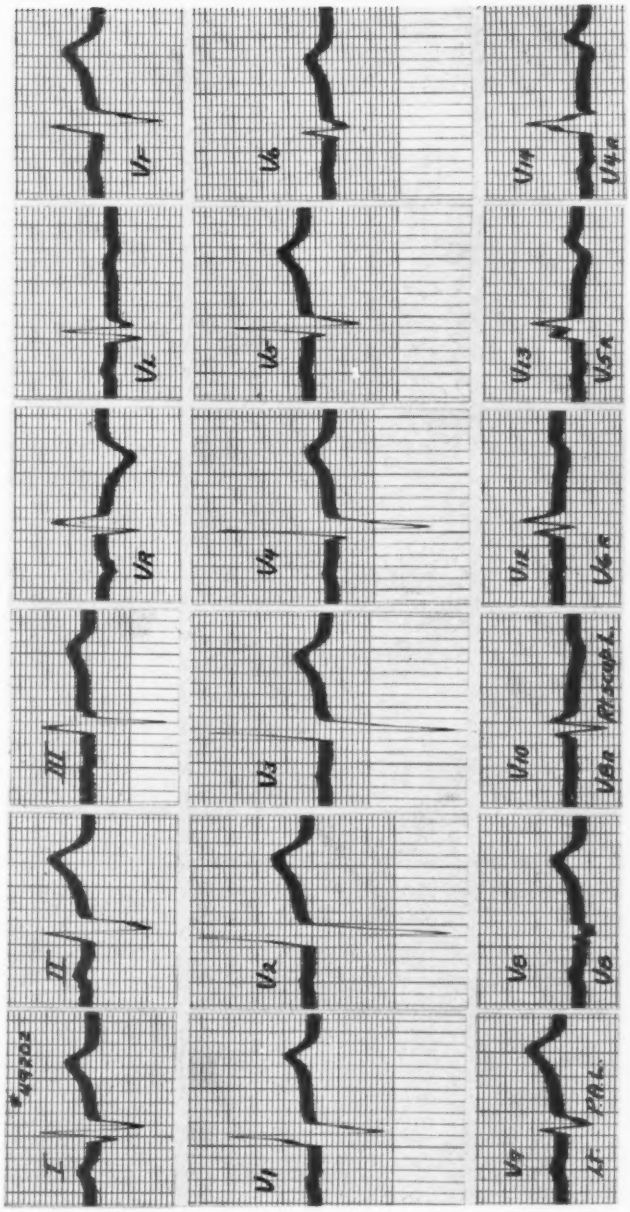

Fig. 5.—Somewhat questionable example of incomplete right branch block in a patient with a congenital heart lesion and right ventricular hypertrophy.

except that the QRS interval did not exceed 0.10 second. Most, if not all, of these have been obtained in cases in which there were clinical reasons for supposing that the right ventricle was carrying an abnormally heavy burden. We are inclined to believe that such tracings represent the combined effect of right ventricular hypertrophy and incomplete right branch block, possibly resulting from the high pressures sustained by this chamber.

Incomplete Left Bundle Branch Block.—This condition is still more difficult to diagnose with confidence than incomplete right branch block. It is probable that it often gives rise to electrocardiograms that are indistinguishable from those considered characteristic of left ventricular hypertrophy. This opinion is supported by an observation made by Dr. John B. Levan. He has been kind enough to send us for teaching purposes the electrocardiogram of a young man who was able to engage in strenuous exercise and appeared to be healthy in every respect. Ordinarily, his electrocardiogram was of the normal type but on one occasion it displayed, off and on, sequential complexes showing pronounced left axis deviation and deeply inverted T deflections in Lead I. The QRS interval of these complexes was slightly longer than that of the normal complexes, and the transitions from the abnormal to the normal mechanism were abrupt. It is evident that disturbances in intraventricular conduction that behave in this manner must involve only a single strand of specialized tissue, for it is hardly likely that several bundles would always cease to function and always recover at the same instant. Transient incomplete left branch block seems, therefore, to be the logical diagnosis in this case.

The electrocardiograms reproduced in Fig. 6 are those of a man, aged 49 years, whose blood pressure had been extremely high for a period of at least five years and who died of congestive cardiac failure in June, 1944. The first tracings, taken on May 23 of that year, are quite characteristic of complete left bundle branch block. The QRS interval measures approximately 0.17 second. On May 29, however, the QRS interval had decreased to between 0.09 and 0.10 second although the QRS deflections of the limb leads still showed conspicuous slurring and notching. The precordial curves of the same date are similar to those obtained in many cases of hypertensive heart disease. Note, however, that no Q wave is present in either Lead V_5 or V_6. We have observed the same sequence of events in a number of other instances. The question arises as to whether the second set of curves represents incomplete left branch block, some other conduction defect, left ventricular hypertrophy alone, or a combination of the last two. If the first is the case, the earliest phases of the QRS complex of the same lead should have exactly the same outline in both sets of tracings. Unfortunately, this valuable criterion is often less useful than might be expected. The delay in the activation of the left ventricle may be nearly as great in incomplete as in complete left branch block or it may be very slight. If the latter is the case, the decision must be made on the basis of the form of the QRS complex during the first 0.01 or 0.02 second of the QRS interval; it will be noted, in the present instance, that in Leads V_1, V_2, V_3, and V_4 the resemblance between the earliest phases of QRS in the two sets of curves is pronounced. In Leads V_5 and V_6,

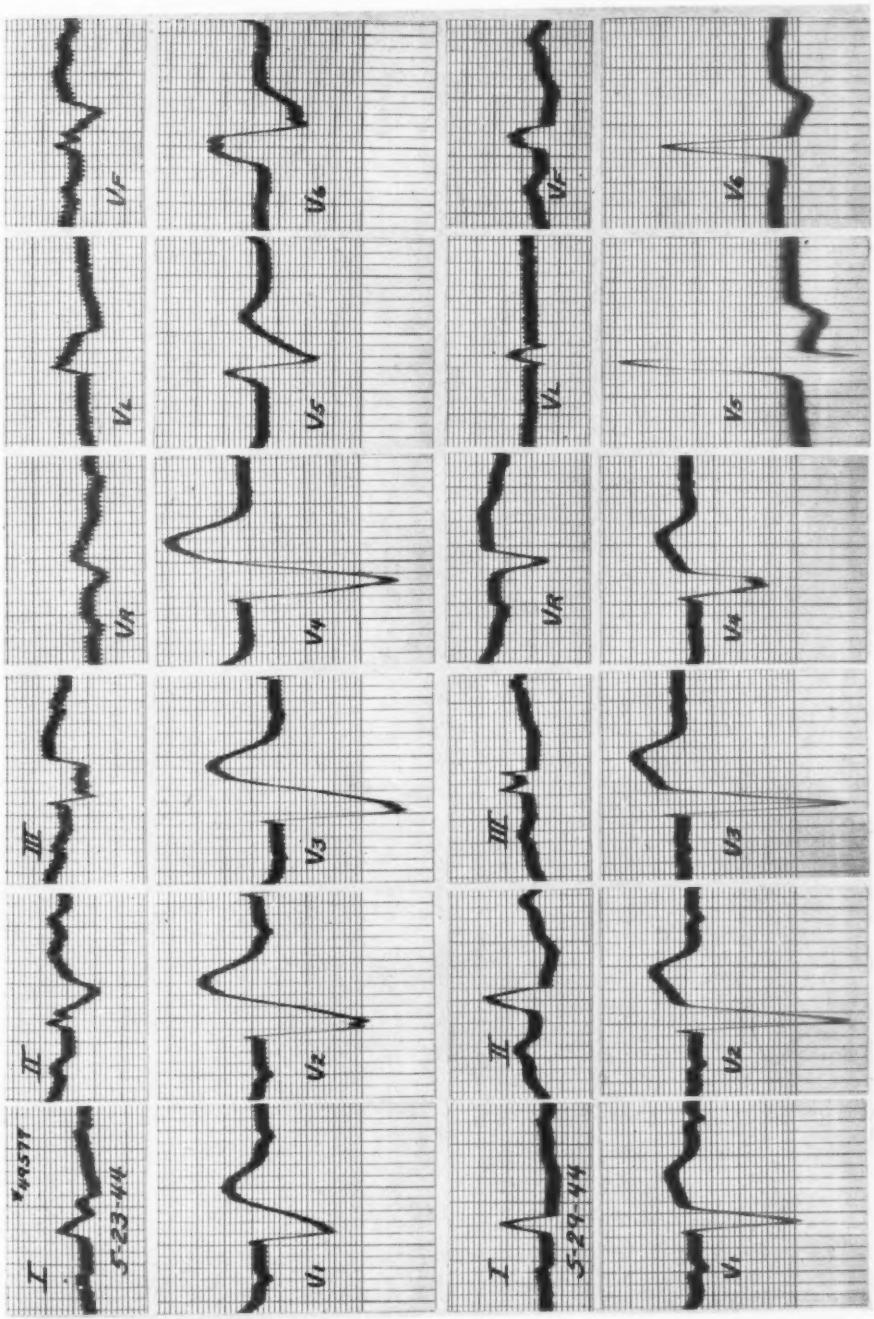

Fig. 6.—Transient complete left bundle branch block in a case of left ventricular hypertrophy possibly complicated by incomplete left bundle branch block.

the R wave begins with a slowly rising portion in the curves of the second set, but the slope of this initial component appears to be much steeper than the corresponding part of the R wave in those of the first set. About the only thing that can be said is that if the last set of tracings represents left ventricular hypertrophy plus incomplete left branch block, the delay in the activation of the left ventricle caused by the latter was slight. If a Q wave were present in the second set of leads from the left side of the precordium, the presence of this conduction defect could be ruled out with reasonable certainty.

In some cases in which incomplete left branch block is suspected, the precordial and extremity curves are like those of complete left branch block in every respect except that the QRS interval is less than 0.12 second.

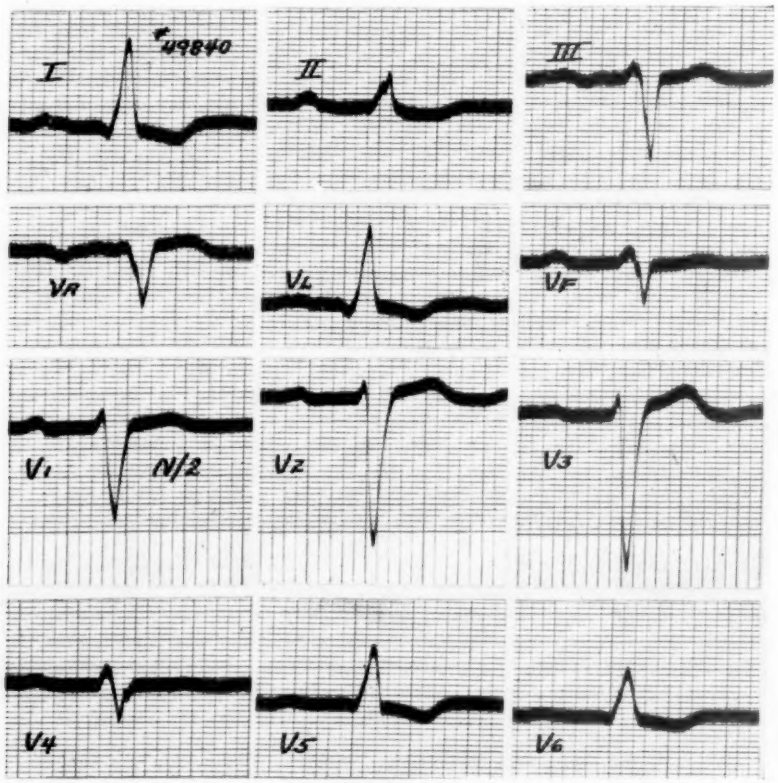

Fig. 7.—Left ventricular hypertrophy possibly complicated by a defect in intraventricular conduction.

Left Ventricular Hypertrophy.—A problem closely related to the one just discussed is presented by the electrocardiogram reproduced in Fig. 7, which is that of a man, aged 35 years, who had mitral stenosis, aortic regurgitation, and pronounced cardiac enlargement. The standard limb leads show conspicuous left axis deviation and inversion of the T wave in Leads I and II. The P-R interval is abnormally long and the QRS interval measures 0.12 second. Because

of the large voltage of the QRS deflections, the precordial leads were taken with the electrocardiograph at one-half its normal sensitivity. There is a conspicuous Q wave in Lead I and a small Q in Lead V_6. The R wave of the last of these leads is not broad-topped or bifid, as it usually is in complete left branch block, but there is some slurring and notching of the QRS deflections of the limb leads. The large voltages recorded in Leads V_1, V_2, and V_3 strongly support the diagnosis of left ventricular hypertrophy, but was this condition present alone, in combination with complete or incomplete left branch block, or in combination with some other conduction defect? In our opinion, the presence of a Q in Lead I and particularly in Lead V_6 plus the absence of a broad-topped or bifid R wave in the latter make the second possibility very unlikely. It is difficult to decide between the other two.

The electrocardiogram reproduced in Fig. 8 is that of a physician, aged 29 years, with mitral stenosis, aortic insufficiency, and pronounced cardiac enlargement. The limb leads show slight right axis deviation and changes in the P waves of the type commonly associated with an advanced mitral lesion. The P-R interval is slightly prolonged and the QRS interval measures approximately 0.105 second. The QRS deflections are slurred. The precordial curves are much more like those seen in left ventricular hypertrophy than like those associated with extreme right ventricular hypertrophy. The voltages of the deflections are not, however, extremely large and the T waves are normal. This electrocardiogram represents either auricular hypertrophy plus left ventricular hypertrophy, or plus hypertrophy of both ventricles. An increase in the QRS interval is rarely encountered in the electrocardiograms which are typical of preponderant right ventricular hypertrophy.

Pulmonary Embolism.—The electrocardiograms shown in Fig. 9 are those of a woman, aged 39 years, who was subjected to a subtotal hysterectomy plus appendectomy on May 26, 1944. On June 6 it was noted that Homans' sign was present, and on the following day at 8 P. M. the patient had a severe attack of chest pain accompanied by faintness and dyspnea. The blood pressure fell to 70/50. The first electrocardiogram was taken at 9:40 P. M. on June 8 and the second was taken at 4:45 P. M. on June 9. The patient died about five hours later and the post-mortem examination showed massive pulmonary embolism, pulmonary arteriosclerosis with organizing and recanalized thrombi, and some active pulmonary arteritis. The heart was not grossly abnormal. The two sets of limb leads are very similar; both show prominent S waves in Lead I and rather conspicuous Q waves in Lead III. The T waves are pointed in Leads II and III and there is a sharp bend in the initial limb of the T complex in Leads I and III. The QRS interval is a little longer in the second set of curves.

The two sets of precordial curves are very different. The first set is notable chiefly for the slight downward RS-T displacement in Leads V_3, V_4, and V_5 and for the sharp angulation of the ascending limb of T in these leads. The second set shows late R waves in Leads V_E and V_1 and sharply inverted T waves in the same leads and is strongly suggestive of incomplete right bundle branch block. It is well known that transient complete right branch block often occurs

in pulmonary embolism and that it is frequently followed by incomplete right branch block of gradually decreasing grade. In many cases, a conduction defect of this sort may account for all of the electrocardiographic abnormalities present. In the present instance, however, there were changes of the kind that have been considered characteristic of pulmonary embolism at a time when the precordial leads showed no evidence of a defect in conduction of the kind in question.

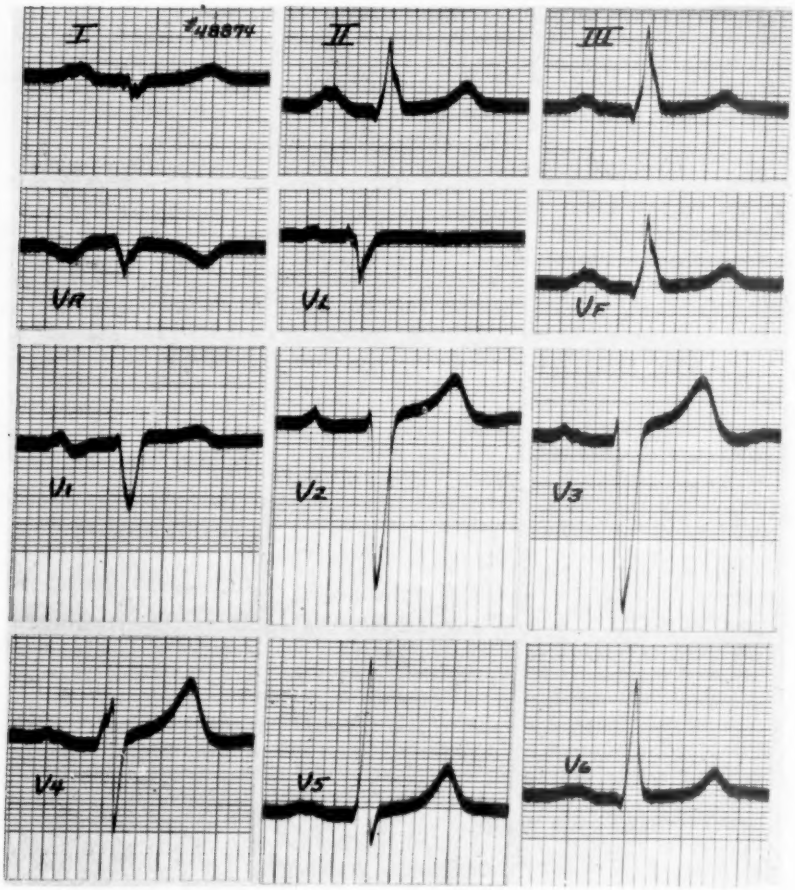

Fig. 8.—Left ventricular hypertrophy or hypertrophy of both ventricles.

Anterior Infarction.—When the anterior wall of the left ventricle is infarcted the resulting changes in the QRS and T complexes are seldom more pronounced in Lead I than in precordial lead V_5. If the anteroseptal wall of the left ventricle is involved, the diagnostic electrocardiographic signs are usually confined to one or more of the first four precordial leads and the complexes of the limb leads are either of the normal type or show modifications of the T waves only. If the anterolateral wall is involved, diagnostic changes are present in Lead I and Lead V_L and in some combination of the precordial leads which includes Lead

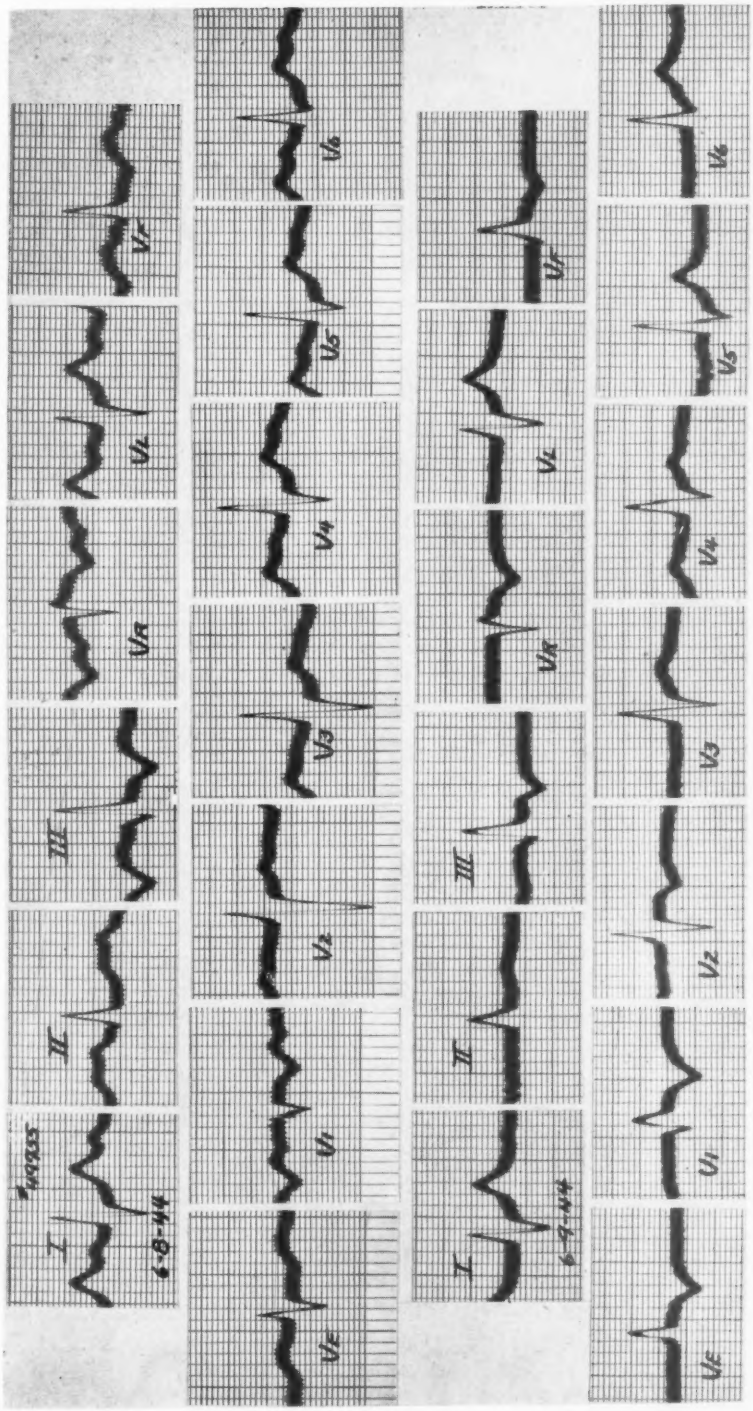

Fig. 9.—Pulmonary embolism.

V_5. There are, however, some striking exceptions to these general rules. We have seen, for example, conspicuous flattening of the T waves in Lead I, terminal inversion of this wave in Lead V_L, and a large pointed positive T wave in Lead III when the complexes of Leads V_1, V_2, and V_3 were diagnostic of infarction and those of Leads V_4, V_5, and V_6 were normal in every respect. More interesting still are those cases in which the complexes of Lead I are diagnostic or very strongly suggestive of anterior infarction while those of the precordial leads are either of the normal type or show only minimal changes of the kind characteristic of this lesion.

The electrocardiograms reproduced in Fig. 10 are those of a man, aged 41 years, who gave a history of severe attacks of chest pain in 1943 and developed a persistent left hemiparesis in May of that year. He had been told that his blood pressure was elevated, but at the time when he was first seen it was only 120/80. The heart was slightly to moderately enlarged; no murmurs were heard. There were no signs of congestive cardiac failure. The extremity curves show conspicuous Q waves and terminal inversion of the T waves in Lead I and Lead V_L. The usual precordial leads are negative except for low R waves preceded by tiny Q waves in V_3 and V_4 and terminal inversion of the T waves in V_3, V_4, and V_5. The leads taken from higher levels, particularly those from the 3rd and 4th intercostal spaces in the left midclavicular and the left anterior axillary line, show considerably more striking changes. The electrocardiograms of this patient differ from those attributed to high lateral infarction in a previous report.[25] The latter showed unusually large R and T waves in the leads from the right side of the precordium. Such changes suggest posterior rather than anterior infarction.

Posterior Infarction.—In some cases of posterior infarction in which there are abnormally large Q waves and sharply inverted T waves in Leads II, III, and V_F, the same kind of changes are present in Lead V_6. The leads from the right side of the precordium may, or may not, display unusually large R waves and tall pointed T waves. Tracings of this kind have been ascribed to infarction of the posterolateral wall of the left ventricle.[25]

The electrocardiogram reproduced in Fig. 11 is that of a man, aged 61 years, who was first seen on June 18, 1944. There was a history of severe chest pain which radiated to both arms in November, 1943. A diagnosis of coronary thrombosis was made at that time and the patient remained in bed for eight weeks. Some days before he was brought to the hospital he had a second attack of chest pain following moderate exertion. A short time after this, tarry stools were noted. At 4:00 A. M. on June 18 he was awakened by severe pain in the region of the left scapula, through the chest, and in the left abdomen. When he was examined some hours later the blood pressure was 70/50, the pulse rate was 130 per minute, and the rectal temperature was 102° F. The heart was enlarged, the heart sounds were faint, and no murmurs were heard. The abdomen was somewhat rigid and tender on the left side. Death occurred at 3:35 P. M. on June 19, shortly after another attack of severe pain in the chest. The location of the infarcted regions disclosed by the post-mortem examination is shown by the sketch reproduced in

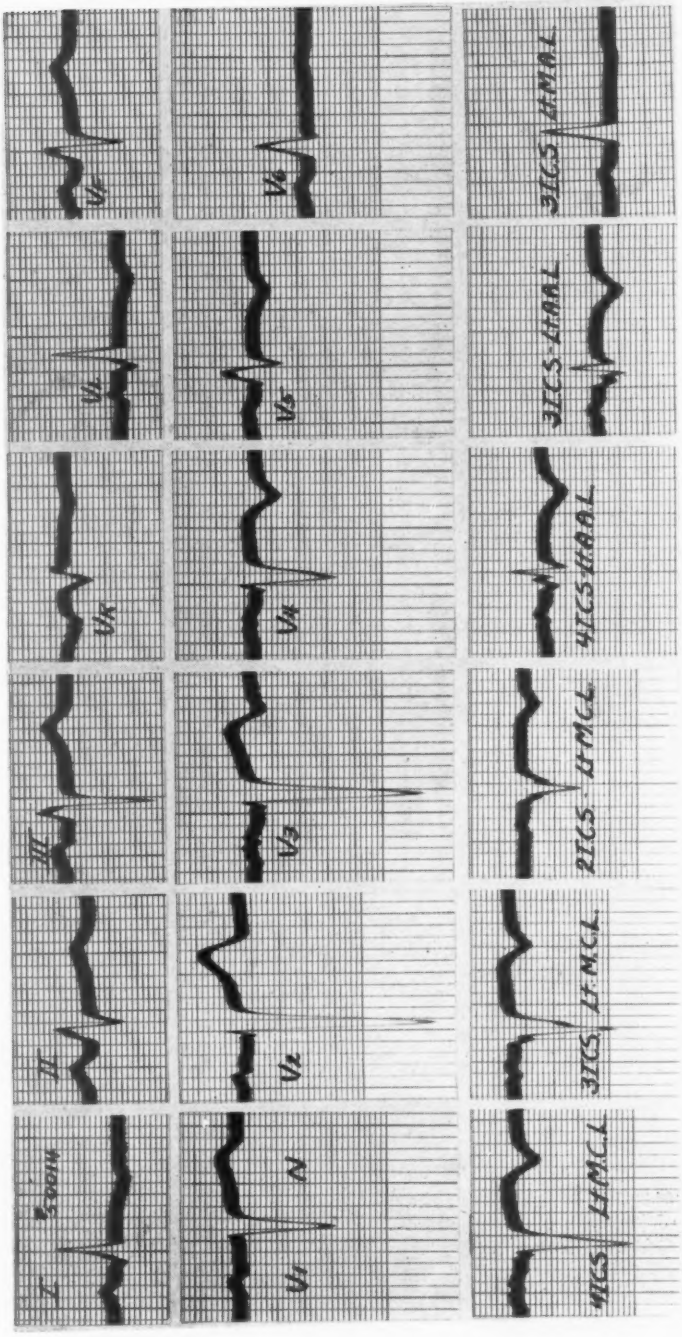

Fig. 10.—Anterior infarction with pronounced signs of infarction in precordial leads from points at higher levels than those from which the standard precordial leads are obtained.

Fig. 12. The autopsy findings included a perforating gastric ulcer complicated by a subphrenic abscess and fibrinopurulent peritonitis.

The electrocardiogram shown in Fig. 13 is that of a man, aged 46 years, who had chest pain of short duration on Sept. 10, 1944. On the following day he had a second attack which lasted one hour. He was then kept in bed, and was told that his blood pressure was 200. He continued to have pain and on September 16 had an unusually severe attack. At the time of the physical examination on the same day, he was still complaining of pain. The blood pressure was

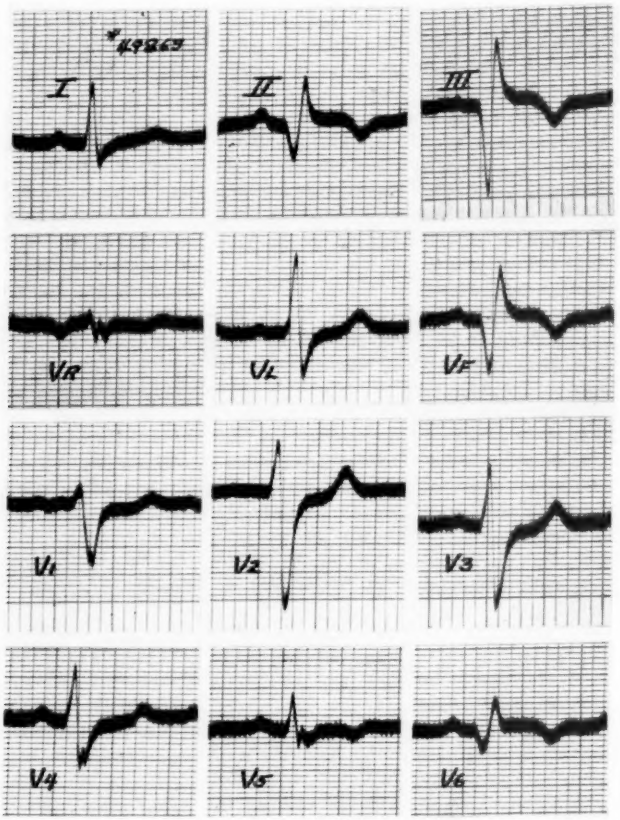

Fig. 11.—Posterolateral infarction.

150/90 and the white blood count was 11,000 per cubic millimeter. The abdomen was distended and tender. The heart was not enlarged, but subsequent roentgenographic studies showed some broadening of the aorta. There was a past history of intermittent claudication, and no pulsation could be felt on palpation of the left dorsalis pedis artery. The patient made a good recovery from the coronary accident.

The first electrocardiograms taken on September 18 were considered within normal limits. There was a slight flattening of the T waves in the limb leads and a slight concavity of the RS-T segment in Leads V_1 and V_2. A number of tracings

taken during the next few days were of similar form. On September 27, however, there was a sharp dip at the end of the T wave in Lead I. The precordial electrocardiogram of the same date shows large pointed upright T waves in Leads V_1, V_2, and V_3 in which these waves had previously been small, and terminal inversion of T in Lead V_6. More striking inversion of T is present in leads from a high point in the left axilla, from the left posterior axillary line at the level of the fourth costosternal junction, and from the left scapular region. These findings suggest that the infarct was on the posterolateral wall of the left ventricle well toward the base. This case illustrates the desirability of taking serial electrocardiograms when the first tracing is negative and of caution in ruling out infarction on the basis of the absence of characteristic electrocardiographic changes.

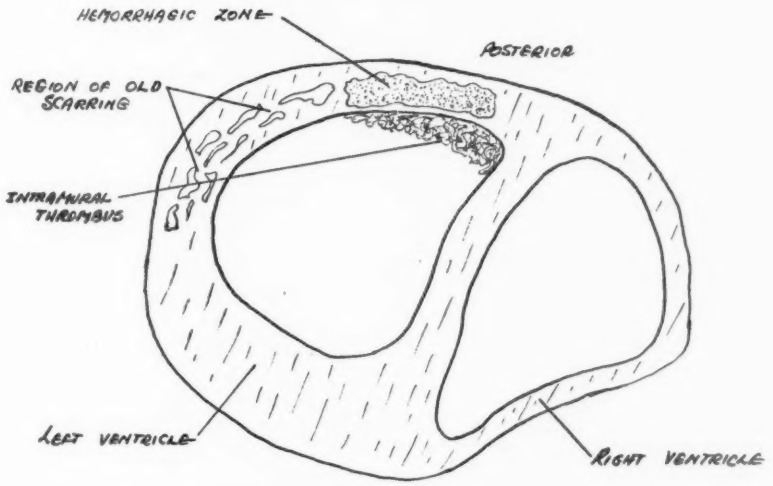

Fig. 12.—Compare with Fig. 11. Location of the infarcted areas found at autopsy.

The electrocardiogram reproduced in Fig. 14 is that of a man, aged 78 years, who was awakened at 2:00 A. M. on Sept. 29, 1944, by severe epigastric pain radiating to the left scapula. The pain was followed by coughing and the expectoration of frothy blood-tinged sputum. When seen at the hospital some hours later, he was cyanotic and the blood pressure was 110/76. On previous examinations the systolic pressure had been in the neighborhood of 150 to 160. The heart was borderline in size; the sounds were extremely faint; no murmurs were heard. Coarse moist râles were audible over the entire lung field. Death occurred about forty-eight hours after the onset of symptoms.

The limb leads are diagnostic of right bundle branch block, but also show large Q waves in Leads II and III and upward RS-T displacement in the last of these leads, which are characteristic of posterior infarction. The precordial leads, however, in addition to the late R waves in Leads V_1, V_2, and V_E, which are attributable to right branch block, show pronounced upward RS-T displacement in these same leads and in Leads V_3 and V_4 as well. These findings suggest antero-

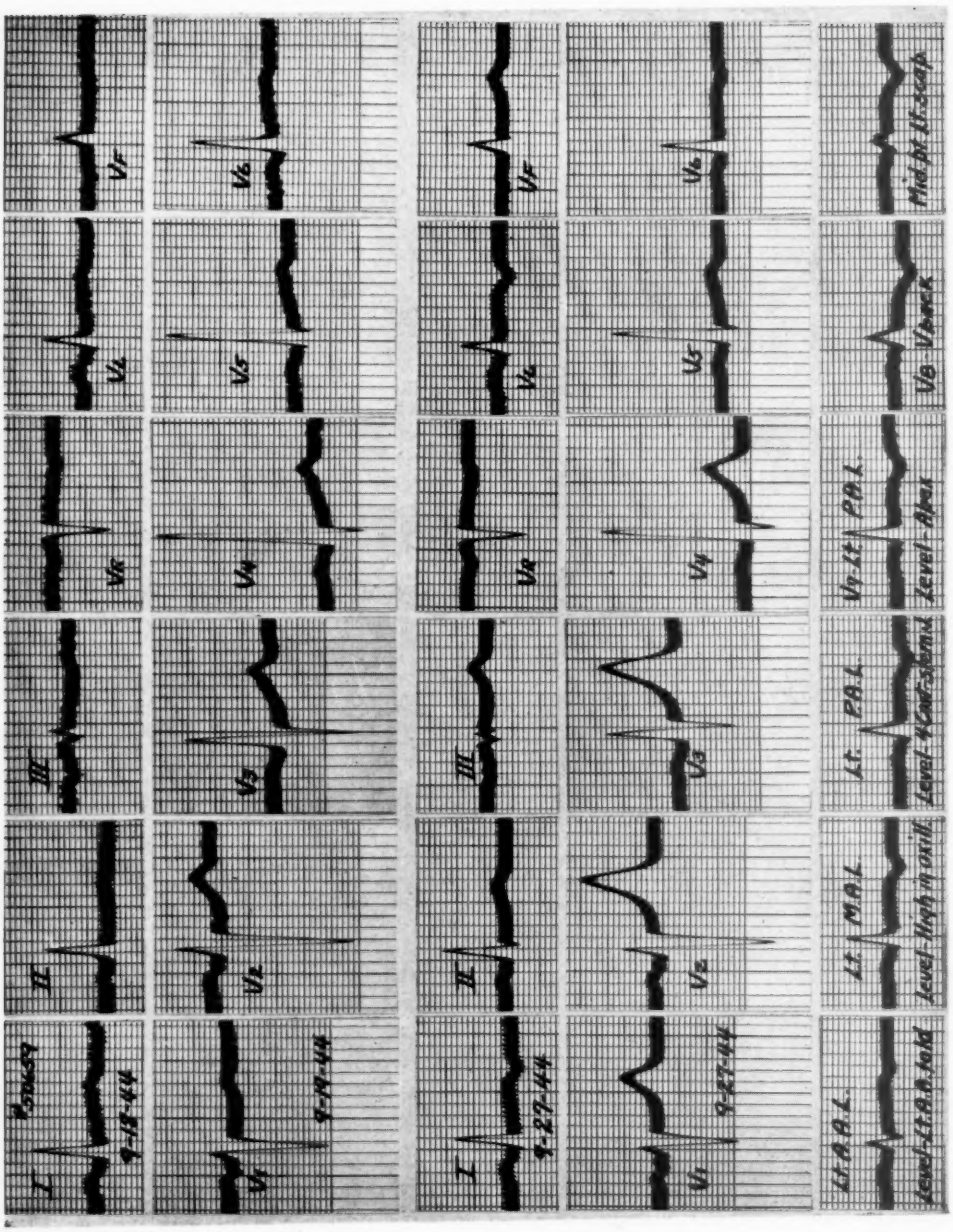

Fig. 13.—High posterolateral infarction. Electrocardiographic evidence of infarction delayed.

Fig. 14.—Right bundle branch block associated with signs of posterior infarction in the limb leads and signs of anteroseptal infarction in the precordial leads.

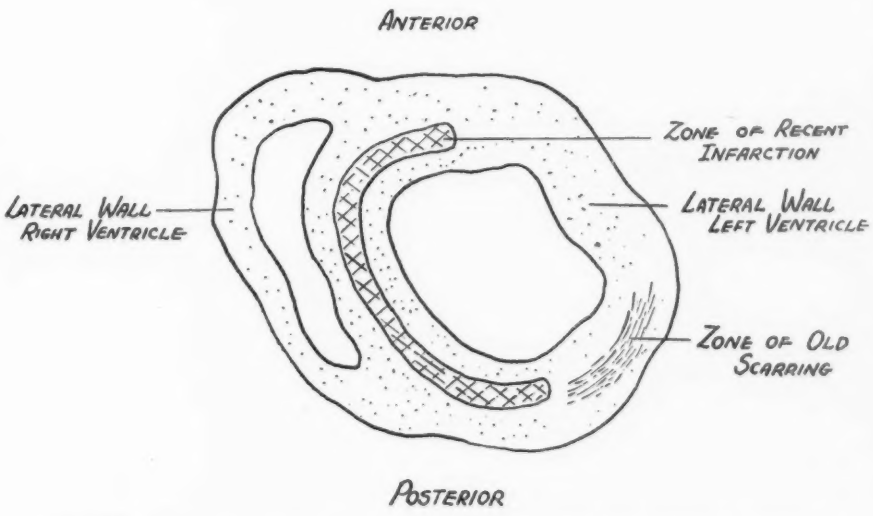

Fig. 15.—Compare with Fig. 14. Location of the infarcted areas found at autopsy.

septal infarction. The location of the infarcted regions disclosed by the post-mortem examination is shown in Fig. 15. Both coronary arteries showed pronounced atherosclerotic changes and the lumen of the anterior descending branch of the left was nearly obliterated. No thrombi were found in these vessels.

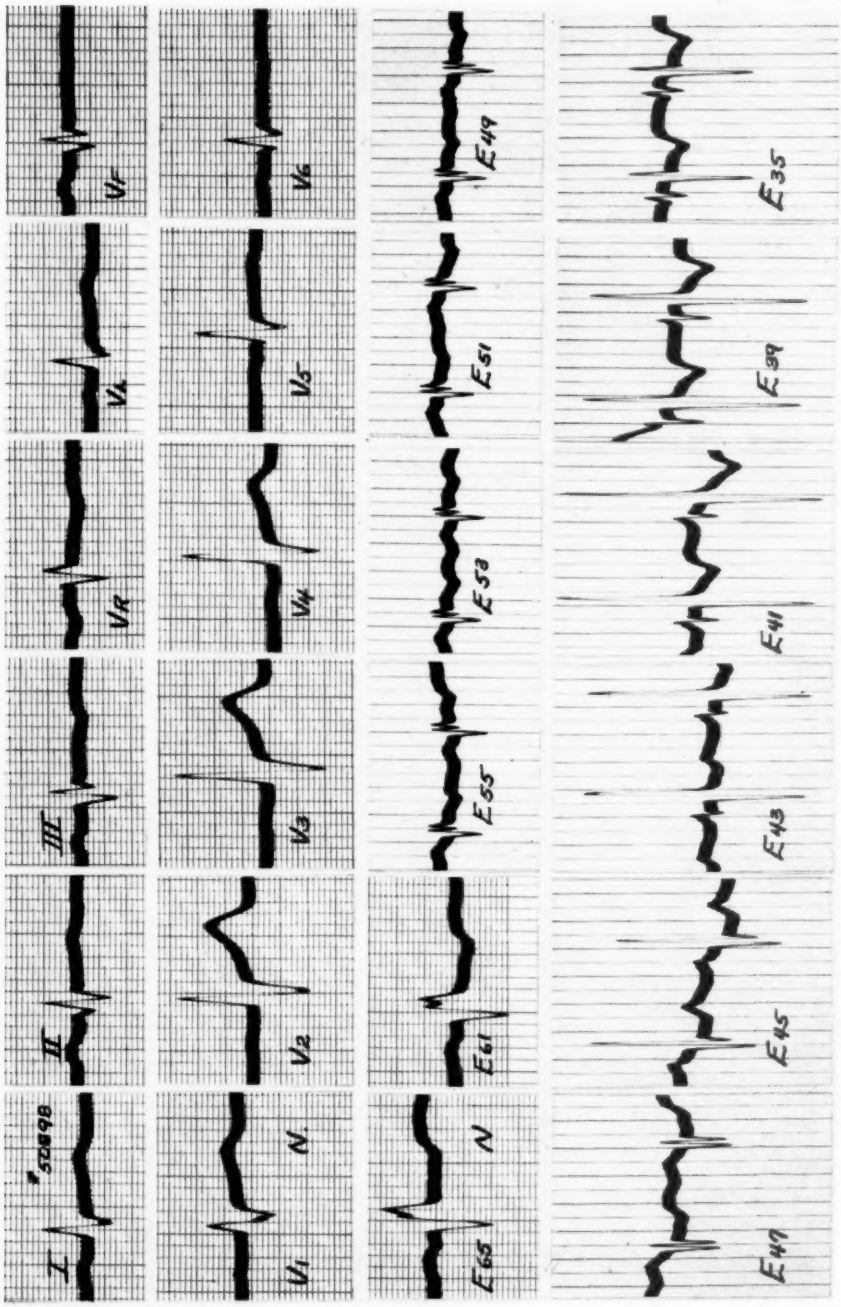

Fig. 16.—Changes suggesting old posterior infarction in a case in which the clinical history made it seem very unlikely that infarction had occurred. The symbol *E* is used to designate an esophageal lead. The numeral attached to this letter gives the distance (in centimeters) of the exploring electrode from the nares.

The electrocardiograms reproduced in Fig. 16 are those of a man, aged 39 years, who had two spontaneous attacks of anginal pain in June, 1944. The first pain was felt in the region of the lower sternum and persisted throughout the day; it was not particularly severe. The second attack occurred about thirty-six hours later; the pain was under the midsternum and lasted for about thirty minutes. Subsequently, there was mild anginal pain on brisk exertion. Physical examination on Sept. 21, 1944, was negative except for a moderately loud late systolic murmur at the apex. The blood pressure was 128/75. There was nothing in the past history which threw any light on the development of angina pectoris.

The electrocardiogram shows large Q waves in Leads II, III, and V_F and in all of the leads from the ventricular levels of the esophagus. There are also rather prominent Q waves in Lead V_6. No changes in the T deflections suggesting myocardial infarction are present, but when such changes are present initially they may disappear in the course of three or four months. We consider the electrocardiograms in this case characteristic of old posterolateral infarction, but a diagnosis of infarction could not be made because standard limb leads taken in 1936 during a physiologic experiment showed exactly the same peculiarities as those taken at the time of our examination. We do not know what the correct explanation of these observations may be. We feel, however, that it is imperative to avoid making a clinical diagnosis on the basis of electrocardiographic examination when, after adequate investigation, it is certain that this diagnosis is not supported by the history and other clinical data.

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THE EFFECT OF SALICYLATES ON ACUTE RHEUMATIC FEVER

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THE most important problem in the treatment of acute rheumatic fever is the prevention of organic heart disease. To effect this it is essential that the rheumatic inflammatory reaction be suppressed in the minimum of time and that polycyclic attacks of rheumatic fever be prevented. If rheumatic attacks were always monocyclic and short lived, severe cardiac damage would rarely occur. For many years salicylates have been used in rheumatic fever in an attempt to attain these objectives. There is general agreement on the rapid antipyretic action of salicylate and on the efficient alleviation of pain and swelling of the joints with salicylate therapy. Whether salicylates prevent polycyclic attacks or reduce the incidence of permanent cardiac damage has been disputed for years.

In 1914, Miller[1] reviewed the literature on the action of salicylates in acute articular rheumatism. He found that with salicylate therapy pain was relieved in an average of 5.3 days; without salicylates pain persisted for 13.4 days. Relapses occurred in 30.3 per cent of the 1,258 patients receiving salicylates, but only 6 per cent of the 974 patients who did not receive salicylates had recurrence of their symptoms. There was no difference in the length of hospital stay in the two groups. Miller quotes Pribram on the incidence of cardiac complications: cardiac damage developed in 28.8 per cent of patients on salicylate and in 23.4 per cent of patients not receiving salicylate. During the period reviewed, Miller states that 15 to 20 grains of sodium salicylate every two or three hours was considered a moderate dose and many physicians gave as much as 300 grains a day. In 1918, Hanzlik, Scott, and Gauchat[2] in a study of the specific effect of salicylates on rheumatic fever concluded that while salicylate is effective it is not specific and that other drugs will produce the same results though perhaps not so consistently. They stated that salicylate was no more than a symptomatic remedy. They found no reduction in the occurrence of endocarditis with salicylate therapy. In 1925, Swift[3] stated that salicylates had a favorable effect on the exudative phase of rheumatic fever but that it failed to influence markedly the proliferative lesions. He felt that this explained why salicylates had no effect on chorea and did not prevent valvular lesions in patients receiving full dosage. He did emphasize that these drugs were of great assistance in reducing the fever and con-

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trolling the "toxic state." The tendency to lose weight was less marked in patients receiving salicylates. With the reduction in fever and toxicity there was a lowering of the heart rate. Swift pointed out that if salicylate eliminated the edema from the valves, as it does from the periarticular tissues, some of the traumatic injury to the endocardium might be eliminated. He emphasized the importance, both to the physician and the patient, of continued care, even after all symptoms are relieved by salicylate therapy, as otherwise the patient may in the end suffer more permanent injury than if he were untreated. In 1933, Graef, Parent, Zitron, and Wyckoff[4] reported a series of 105 cases of acute rheumatic fever treated only with opiates and local therapy to the affected joints. They stressed the tendency of the acute manifestations of rheumatic fever to subside spontaneously and often rapidly.

In 1943, Coburn[5] reopened the problem of salicylate therapy in rheumatic fever in his report of 101 cases treated with varying amounts of sodium salicylate. Sixty-three patients received only small doses of the drug, and 21 developed organic heart disease. Thirty-eight received 10 Gm. or more of sodium salicylate daily, and none of these developed heart disease. Coburn administered sodium salicylate by mouth and also intravenously in doses of 10 to 20 Gm. daily. He felt that by giving the medication by vein, a more rapid and sustained rise in the plasma concentration of the drug was obtained. His studies were controlled by estimations of the plasma level. He concluded that a plasma salicylate level of at least 35 mg. per 100 c.c. may be required to suppress the rheumatic reaction and that plasma levels below 20 mg. per 100 c.c. may be sufficient to relieve symptoms while masking a progressive inflammatory process.*

Hanzlik[6] credits Mendel with the first use of intravenous salicylate in 1904. Hanzlik[6] quotes Matta, Lesne, Gilbert, Coury, and Bernard as using this method of administration. These clinicians claimed certain advantages in the intravenous method over the oral route: namely, the avoidance of gastric disturbances, emesis, and side reactions in general; more rapid absorption of the drug; and finally the prevention of cardiac complications. Coburn has revived the interest in this method and claims that a more rapid elevation of the blood salicylate is obtained and that the patient is more quickly brought under control.

McEachern[7] has reported his results in 350 cases of acute rheumatic fever treated between November, 1943, and June, 1944. Toxic reactions were frequent with intravenous medication and minimal in the orally treated group. Cardiac sequelae were present in both groups. He concluded that oral administration of 10 to 16 Gm. of sodium salicylate was the most satisfactory method of treatment. Taran and Jacobs[8] concluded that intravenous salicylate offered no advantages in treatment and that the technical difficulties and annoying symptoms outweighed the possible benefits of a more rapid rise in the plasma salicylate level.

Hanzlik,[6] Goodman and Gilman,[9] and, more recently, P. K. Smith[10] have concluded that intravenous administration is unwarranted because of the rapid and almost complete absorption of sodium salicylate from the gastrointestinal tract. Smith has shown that peak plasma levels are reached about one hour after

*Coburn introduced the term *gamma per cubic centimeter* for salicylate levels. We feel that such terminology may be confusing and prefer to retain the more familiar *milligram per 100 c.c.* for the sake of clarity.

oral administration. Hanzlik states that the advantages claimed by the supporters of the intravenous method are unsupported by any evidence and that, when administered in this way, salicylate may cause considerable damage to the heart and other important organs.

In June, 1945, Keith and Ross[11] reported their results in the treatment of two groups of patients with acute rheumatic fever in the Royal Canadian Navy. The sedimentation rate returned to normal in an average of four weeks in a group of 70 patients receiving 10 to 13.3 Gm. of salicylate per day and in four and one-half weeks in 33 patients receiving 0 to 1.7 Gm. a day. Three patients in the low dosage group and five in the high salicylate dosage group developed heart disease. Five patients who had pre-existing heart disease showed progression, two in the low and three in the high salicylate group. They could not conclude that large amounts of salicylates were of any more benefit than small doses. Taran and Jacobs[8] recently reported their experience with large doses of salicylate. They concluded that large doses of salicylate brought about prompt and effective response both in patients with polyarthritis without carditis and in those patients with carditis. They state that if therapy is not instituted promptly activity continues for many weeks. Small doses of salicylate in their experience had no more effect than no salicylate at all in patients with carditis. Murphy,[12] in a recent report of careful studies in twelve patients receiving large doses of salicylate, questions the usually accepted view that salicylates promote the subsidence of rheumatic joint inflammation. In several patients characteristic lesions developed in a variety of sites during the course of heavy salicylate therapy. It is obvious that there is still no agreement as to the efficiency of salicylate in preventing cardiac damage or the ability of large doses to reduce rheumatic activity more quickly than small amounts.

METHODS OF STUDY

We have observed 186 cases of acute rheumatic fever in young adults between November, 1942, and September, 1945. These patients have been observed under three different therapeutic regimes. Some have been treated with small doses of salicylate given only to relieve symptoms. Others received large doses by mouth until all evidence of rheumatic activity had subsided. A third group received sodium salicylate intravenously for one week and then large oral doses. We wish to report our experience with these three types of treatment considering the effect on the length of rheumatic activity, on polycyclic attacks, on pericarditis, and on the occurrence of permanent cardiac damage.

The diagnosis in each case was carefully determined and in all cases the criteria established by Jones[13] were applied. In each case, before therapy was started, a complete history was taken and a physical examination was made; other studies made on each patient included an electrocardiogram, an x-ray of the heart, hemoglobin determination, erythrocyte count, leucocyte and differential counts, urine examination, and erythrocyte sedimentation rate. A twenty-four hour period of observation was used in most cases before starting therapy and in a few cases three days to two weeks of observation took place

before the diagnosis was accepted and therapy was started. Routine urine examinations were done once weekly. Certain patients with acute rheumatic fever were not included in this study, because of the occurrence of purulent complications which would influence the sedimentation rate and fever. The patients with pneumonitis are included except where sputum examination and the clinical course indicated that it was not of rheumatic origin. In all cases studied from November, 1943, on, sedimentation rates were done two or three times weekly for two to four weeks and then once weekly; electrocardiograms were taken two or three times weekly for two weeks and then once weekly. The patients studied in 1942 and 1943 received these tests less often. In 1942 and 1943 the Wintrobe method was used in determining the sedimentation rate, but after January, 1944, the Westergren method was used, without correction for the cell volume. This was not necessary as no significant anemias were encountered. Hemoglobin, red blood cell counts, and leucocyte counts were done twice monthly. In many of the later cases antistreptolysin determinations were done to assist in establishing a diagnosis. All but two of the patients were men. The age range was 18 to 40 years; 70 per cent were under 25 years and 87 per cent were under 30 years of age. There were no significant differences in the age composition of the three treatment groups. Fifty-one per cent of those receiving small doses and 39 per cent of those receiving large doses had a history of previous rheumatic fever. Pre-existing rheumatic valvular heart disease was present in 12.5 per cent of the small dose group and in 5 per cent of the large dose group. The differences in these proportions are not statistically significant.

Eighty-eight patients were treated with small doses, ranging from 2 to 7 Gm. a day. The drug was given until nausea or tinnitus developed or until relief of symptoms was obtained, and the dose was reduced markedly or it was eliminated entirely when the pain and fever had subsided, regardless of the level of the sedimentation rate. Sodium bicarbonate was usually given in equal doses. The medication was given four to eight times during the day from 8:00 A. M. to 10:00 P. M. In some cases acetyl salicylic acid was used and in others sodium salicylate. Sixty-four patients treated by this method were admitted during the winter of 1942-1943, 17 in the winter of 1943-1944, and 7 in 1944-1945.

Fifty patients were treated with 10 to 16 Gm. of sodium salicylate per day by mouth. The medication was divided into equal doses and given at four-hour intervals throughout the twenty-four hours. Sodium bicarbonate was given when necessary to reduce gastric irritation and to prevent toxic reactions. Plasma salicylate determinations were done several times weekly and the dosage was adjusted to maintain levels of 35 to 45 mg. per 100 cubic centimeters. The salicylate was continued in this dosage until the sedimentation rate had maintained a normal level for at least two weeks. If the sedimentation rate rose after salicylate was stopped, the drug was again given in the same dosage until the sedimentation rate again remained normal for two weeks. In some cases salicylate was omitted for several days because of a high plasma level or because of toxic symptoms.

Forty-eight patients were given 10 Gm. of sodium salicylate in 1,000 c.c. of normal saline daily for seven days. The infusion was administered slowly over a six to eight-hour period. In several cases doses of 14 and 20 Gm. were given for one or several days because of continued symptoms. The day following the last intravenous injection these patients were started on 10 to 16 Gm. of sodium salicylate by mouth daily and continued as in the large oral dosage group. Plasma salicylate levels were determined several times weekly in this group. The patients treated with large doses of sodium salicylate were observed from March, 1944, through the remainder of the study.

THE EFFECT ON THE SEDIMENTATION RATE

The erythrocyte sedimentation rate, while a nonspecific test, has been accepted as a sensitive indicator of rheumatic activity. Most authorities agree that physical activity should be limited until the sedimentation rate has reached a normal level. The comparative effects of the three methods of treatment on the sedimentation rate should be indicative of the relative effect on rheumatic activity.

The sedimentation rate may show wide fluctuations in acute rheumatic fever as the inflammatory process varies in intensity. A certain number, those with monocyclic attacks, will show a prompt drop in the rate to a normal level (Fig. 1, Patient H. P.). If these patients are used to show the effect of salicylate therapy it will indicate a marked effect. Some patients may show an apparent response but then continue with lower but abnormal sedimentation rates suggesting a repression of rheumatic activity by salicylate (Fig. 1, Patient A. E.). Other patients will have polycyclic attacks with recurring waves of activity. Here, if salicylate is given with the rate elevated, it will show an effect as the rate falls. If it is then omitted the rise in rate suggests that salicylate was stopped too quickly. However, in Fig. 2, Patient A. D., it is seen that this may occur regardless of salicylate therapy with so-called adequate blood levels. Some patients show continuous rheumatic activity with wide fluctuations of the sedimentation rate uninfluenced by adequate plasma salicylate levels (Fig. 2, Patient R. N.). Graef, Parent, Zitron, and Wyckoff[4] have stressed these variations in duration of activity and the tendency of acute manifestations to subside spontaneously in the course of untreated rheumatic fever. Ernstene[14] found that frequently the sedimentation rate increased slightly after stopping salicylate and then dropped promptly to the previous level.

In order to take into consideration these fluctuations in rheumatic activity and the effect of salicylate therapy on the disease, we have added the days in which the sedimentation rate was above 20 mm. per hour to obtain the total days elevation for each case. An average number of days of elevated sedimentation rate was then determined for each treatment schedule. These averages have been subjected to statistical analysis to determine the significance of the differences under the three plans of treatment.

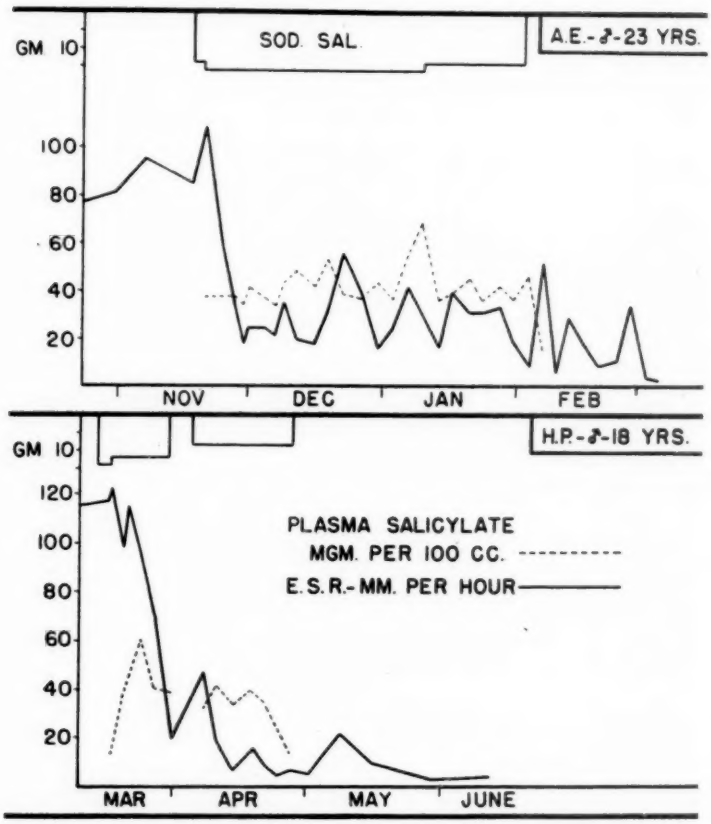

Fig. 1.—Patients A. E. and H. P. The chart shows the relationship of the erythrocyte sedimentation rate, plasma salicylate levels, and the dose of sodium salicylate by mouth.

In an effort to separate the severe cases from those with mild rheumatic inflammation, we have divided the cases into two groups; those with sedimentation rates of 60 mm. per hour or less and those with higher rates.

One hundred twenty-six cases were observed where the highest sedimentation rate was over 60 mm. per hour. Table I shows the average number of days of elevated sedimentation rates in the three treatment groups. There is a range of ten days between the large oral dosage and the intravenous groups with the small dose group falling between the two. Statistically, the difference of these means is not significant and we can conclude that in these three groups there was no more rapid reduction of rheumatic activity with large than with small amounts of salicylate.

Sixty cases were studied where the highest sedimentation rate was under 61 mm. per hour. Fifty-one patients received small doses of salicylate and had elevated sedimentation rates for an average of 35.2 days. There were only four

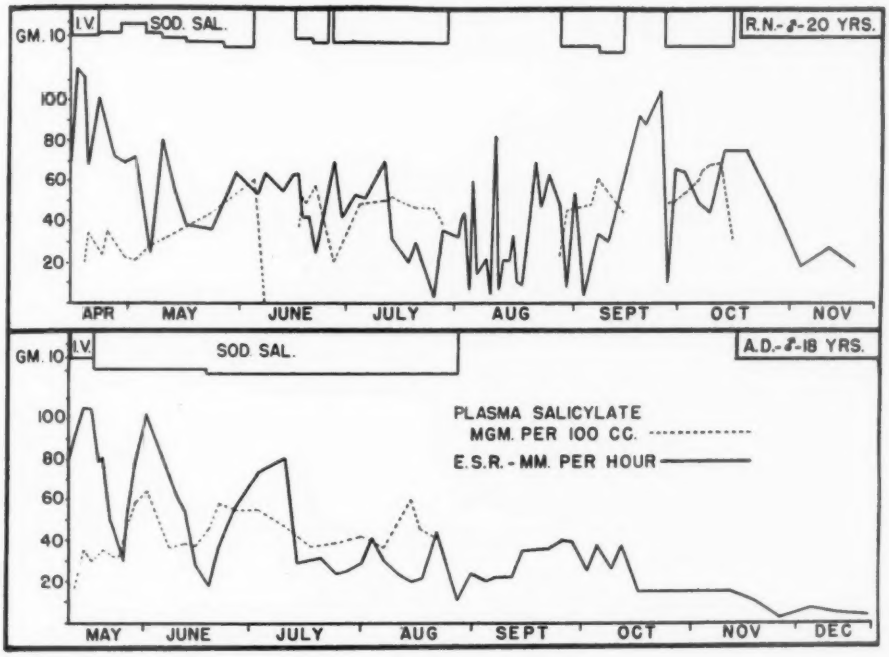

Fig. 2.—Patients R. N. and A. D. The chart shows the relationship of the erythrocyte sedimentation rates, plasma salicylate levels, and the dose of sodium salicylate intravenously and by mouth.

TABLE I. THE EFFECT OF SALICYLATE ON THE ERYTHROCYTE SEDIMENTATION RATE

	CASES	MEAN DAYS ELEVATED E. S. R.
E. S. R. over 60 mm./hour*		
Small oral	37	58.7
Large oral	45	51.3
Intravenous	44	61.4
E. S. R. under 60 mm./hour		
Small oral	51	35.2
Large oral	5	36
Intravenous	4	27.8
All Cases		
Small oral	88	45.1
Large oral	50	49.8
Intravenous	48	58.6
Total large and oral and intravenous	98	54.1

*E. S. R.=erythrocyte sedimentation rate.

patients who received intravenous therapy and five who received large oral doses in this group, too few to offer any accurate comparison in effectiveness of therapy (Table I).

Table I also shows the consolidated data for all cases observed, both high and low sedimentation rate groups. Here the greatest difference between the means is 13.5 days, between the small dose and the intravenous therapy group. Here again, by statistical analysis there is no significant difference between the average days of elevated sedimentation rate for the three treatment groups. If we consider all the large dosage patients, both oral and intravenous, the average number of days of elevated sedimentation rate is 54.1. The difference between this average and that for the small dose group is nine days, again not a statistically significant difference. The median for the small dose group was just over six weeks while the median for the large dosage group was also six weeks.

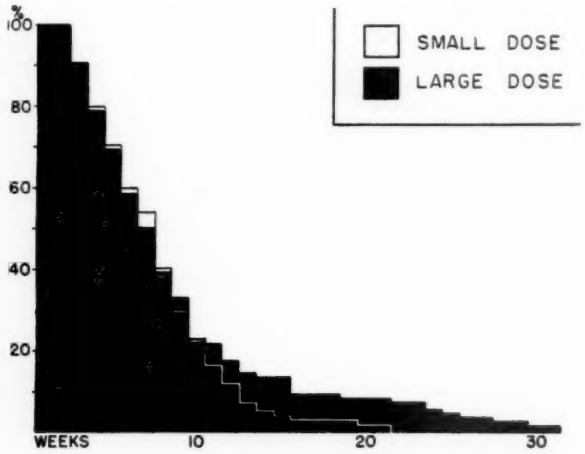

Fig. 3.—The percentage of cases with elevated sedimentation rates, by weeks, under treatment with small and with large doses of salicylate.

The higher average days resulted from seven patients with sedimentation rates which remained elevated for more than twenty-two weeks. Fig. 3 shows the proportion of the total small and large dose groups with elevated sedimentation rates in consecutive weeks of observation. Here it can be seen that actually there is no real difference. The two curves follow each other almost exactly except for those cases with prolonged activity which perhaps by chance occurred only in the last two seasons and were treated with large doses. In any event from our data it is seen that large doses of salicylate are no more effective than small doses in reducing an elevated sedimentation rate.

THE EFFECT ON FEVER

The data on the effect on the temperature are based on oral temperature as recorded by the ward nurses in a routine manner. Temperatures were taken four times daily during the period of acute illness and then twice daily, at 8:00 A. M. and 4:00 P. M. One hundred seventy-one patients showed a temperature of

TABLE II. THE EFFECT OF SALICYLATE ON THE NUMBER OF DAYS OF FEVER

	CASES	MEAN DAYS OF FEVER
Small oral	82	11.63
Large oral	44	3.77
Intravenous	45	4.57
Total large, oral and intravenous	89	4.16

99.2° F. or more on at least one occasion. Table II shows the average number of days of fever in the three treatment groups. The greatest difference is 7.8 days between the small and the large oral treatment groups. Between the intravenous and the small therapy group is a difference of seven days. By statistical analysis both of these differences are significant, and we can conclude that large doses of salicylate will reduce the temperature to normal more quickly than small doses. It is also evident that oral, large dose therapy is more effective than the intravenous method. Fig. 4 shows the proportion of the small and total large dose (both oral and intravenous) groups with fever in consecutive days of observation. Here again, the advantage of using large doses of salicylate in eliminating the febrile reaction is evident.

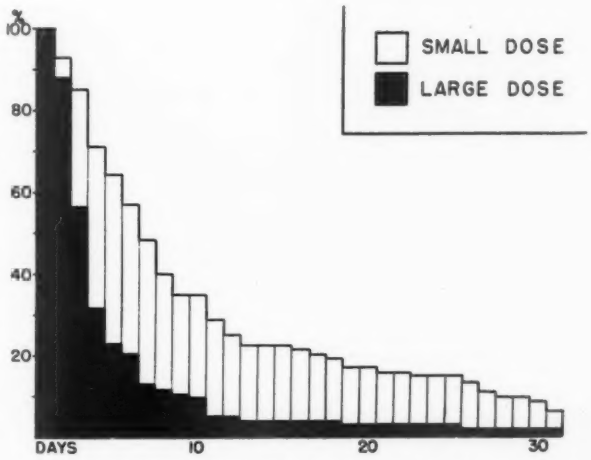

Fig. 4.—The percentage of cases with fever, by days, under treatment with small and large doses of salicylate.

THE EFFECT ON POLYCYCLIC ATTACKS

Coburn[5] has pointed out the difficulty in determining whether any form of treatment has a therapeutic effect in rheumatic fever. About 20 per cent of young adults may be expected to have monocyclic attacks and recover spontaneously in about three weeks with symptomatic therapy. We have tabulated the data on polycyclic attacks in our group and included every patient who showed a

TABLE III. THE EFFECT OF SALICYLATE ON POLYCYCLIC RHEUMATIC FEVER

	TOTAL CASES	POLYCYCLIC CASES	%
E. S. R. over 60 mm./hour			
Small oral	37	19	51.3
Large oral	45	28	62.1
Intravenous	44	28	63.6
E. S. R. under 60 mm./hour			
Small oral	51	16	31.2
Large oral	5	2	
Intravenous	4	2	
All Cases			
Small oral	88	35	39.8
Large oral	50	30	60
Intravenous	48	30	62.5
Total large, oral and intravenous	98	60	61.3

secondary elevation in sedimentation rate after the rate had reached a normal level (Table III). In some patients there were, in addition, clinical signs and symptoms indicating rheumatic activity. Thirty-five patients, 39.8 per cent of all those receiving small doses, showed such polycyclic manifestations. Thirty patients, 60 per cent of all patients receiving large oral doses, and 30 patients, 62.5 per cent of all receiving intravenous therapy, showed polycyclic attacks. The difference of these means is statistically significant. In our experience large dose therapy does not reduce the occurrence of polycyclic attacks. It is interesting to note that Miller,[1] in his review in 1914, found a similar effect with salicylate therapy. Of the patients of his series receiving salicylate, 30.3 per cent had relapses while only 6 per cent of those not receiving the drug suffered such polycyclic attacks.

THE EFFECT ON VALVULAR HEART DISEASE

The most important factor in determining the efficacy of various types of therapy is the prevention of valvular heart disease. This is a difficult problem to evaluate in a short study such as this. To be certain one should re-examine these patients several years after the attack of rheumatic fever. The problem of the evaluation of a systolic apical murmur is an important aspect of this question. When a patient is admitted to the hospital with an aortic diastolic

or mitral systolic murmur it is frequently impossible to say how long these murmurs have been present. As a rule, it can be assumed that the murmurs were present before. Furthermore, it is difficult to tell whether the present attack has produced additional cardiac damage or not. We have used Levine's[15] method of grading systolic murmurs throughout this study. Levine states that several observers will vary no more than one grade in classifying murmurs under this system so that a variation of two grades indicates an actual change. For example, a progression from a Grade 1 to a Grade 3 systolic murmur is evidence of actual change in volume of the murmur and, unless associated with elevation of temperature and tachycardia, can be interpreted as evidence of an organic change. Increase in cardiac size under observation is another evidence of increased cardiac damage.

Due to the limited period of observation, any data on the development of cardiac damage we now have are obviously incomplete. However, we can answer the question of the development of cardiac damage with Coburn's large dose method. Fourteen patients in the entire series developed evidence of organic heart disease or showed increased damage of pre-existing heart disease (Table IV).

TABLE IV. THE EFFECT OF SALICYLATE ON THE DEVELOPMENT OF VALVULAR HEART DISEASE

	SMALL DOSE	LARGE DOSE
Aortic insufficiency	2 cases	2 cases
Mitral stenosis	1 case	2 cases
Probable mitral insufficiency	3 cases	3 cases

There were seven patients who developed new cardiac murmurs or showed evidence of increased damage of pre-existing heart disease while receiving large doses of salicylate. Five were given large doses by mouth and two received intravenous therapy. Five of these men had a past history of rheumatic fever. There were two patients who developed aortic insufficiency, one with a past history of rheumatic fever and one without such a history. One received intravenous therapy and one oral. There is no question but that these two men developed valvular heart disease while receiving large doses of salicylate. Two patients receiving large oral doses developed mitral stenosis under observation where no presystolic murmur had been heard on admission. Both patients, however, had a past history of rheumatic fever. The remaining three men were admitted with no cardiac murmurs. They developed persisent Grade 2 apical systolic murmurs. All three gave a past history suggesting previous rheumatic fever.

There were also seven men receiving small doses of salicylates who developed organic heart disease or showed signs of increased damage of an old lesion. Here again two patients developed aortic insufficiency, neither man having a past history of rheumatic fever. One patient developed a presystolic apical murmur and showed an increase in the intensity of a pre-existing apical systolic

murmur. Two patients developed persistent Grade 2 apical systolic murmurs where none existed on admission. Only one of these men had a past history of rheumatic fever. The sixth man on admission had a soft Grade 1 apical systolic murmur which progressed to a rough Grade 3 murmur by the time of discharge. The seventh patient was admitted with mitral stenosis and insufficiency and auricular fibrillation of long standing. He had a mild attack of rheumatic fever but there was possible further cardiac enlargement as the transverse cardiac diameter by x-ray examination increased one centimeter. All of these patients had received small amounts of salicylate but had remained on limited physical activity until the sedimentation rate had remained at a normal level for at least several weeks.

We can conclude, then, that large doses of salicylate will not prevent the occurrence of valvular heart disease or the progression of pre-existing cardiac damage. In our experience there was the same incidence of heart disease in the two groups under observation. Because of the short period of observation, we are not in a position to state that either one or the other method of therapy will lessen cardiac damage.

THE EFFECT ON PERICARDITIS

It is probable that large amounts of salicylate will relieve the joint pain and discomfort more quickly than small doses. We have no statistical data on this aspect of the problem but in using large doses we had little or no difficulty in relieving the symptoms within one to three days. A more certain test of this is the effect on acute pericarditis. There were three cases with acute pericarditis treated by intravenous therapy and one treated with large oral doses of salicylate. Three occurred in the winter of 1944 and one occurred in 1945. The longest period of elevated sedimentation rate was thirty-three days; the average was twenty-six days. The longest period of fever was six days; the average was four. One of these patients developed aortic insufficiency. However, the effect of large dose salicylate therapy was striking. There was rapid subsidence of all joint and chest pain and fever. This was in marked contrast to the cases of pericarditis of the previous season which were treated with small doses of salicylate. Two of these four patients received sulfadiazine because of the presence of pneumonitis and pericarditis and the possibility of a bacterial infection. One of the two also received penicillin for thirty-six hours. In each case there was no effect from the antibiotics but a prompt response to salicylate.

In the fall and winter of 1942-1943, we had seven cases of acute pericarditis treated with small doses of salicylate. The average period of elevation of the sedimentation rate in this group was forty-four days with a range of fifteen to seventy-seven days. Fever was maintained for as long as thirty-four days in one case; the average was twenty-one days. Several of these boys were acutely ill for several weeks. Two of the seven are not included in the averages given because of the development of complications which would influence sedimentation rate and fever. One died in cardiac failure; this was our only death from acute rheumatic fever. Post-mortem examination showed complete obliteration of

the pericardial cavity, multiple areas of pulmonary infarction, and thrombophlebitis of the prostatic venous plexus. The second patient developed an acute empyema during the course of his rheumatic fever, which necessitated thoracotomy and prolonged drainage.

It would appear from our experience that the use of large amounts of salicylate will relieve the symptoms and cause more rapid subsidence of acute pericarditis than will small doses. This in itself would be a definite factor in support of large doses. However, we had only four patients treated with large doses. Moreover, the two groups did not occur in the same season, and it is well known that rheumatic fever varies in severity from one season to another. Despite these criticisms, we have been impressed with the prompt control of pericarditis with large dose therapy.

THE EFFECT ON THE P-R INTERVAL

The occurrence of a prolonged P-R interval in the electrocardiogram is accepted as the most frequent and important electrocardiographic manifestation of acute rheumatic fever. The effect on this sign of cardiac involvement would be helpful in evaluating the efficiency of salicylate therapy. Wyckoff, DeGraff, and Parent[16] have reported careful studies on this problem in eight patients receiving salicylate and ten receiving no therapy. They found that the P-R interval showed wide and inconstant variation uninfluenced by salicylate in doses of 8 Gm. per day. For accurate appraisal of this phase of the problem electrocardiograms should be taken daily. Many of the patients studied in 1943 did not have frequent electrocardiograms. In some cases three weeks elapsed between tracings. However, by presenting our data by weeks some information can be deduced. A total of 47 patients showed a prolonged P-R interval of over 0.22 seconds, or A-V dissociation. Seventeen patients receiving small doses of salicylate showed prolonged P-R intervals and 52.9 per cent of them showed a normal P-R interval by the end of two weeks. However, many of these patients did not have electrocardiograms at intervals close enough to allow accurate evaluation. Five of the patients receiving small doses, whose tracings were taken frequently, required an average of ten days for the P-R interval to reach normal. Eighty per cent had a normal P-R interval at the end of one week. In 81.2 per cent of those receiving large oral doses and in 78.5 per cent of those receiving intravenous therapy the P-R intervals had returned to normal at the end of two weeks. While our data are not sufficient to conclude unequivocally that small doses are as efficacious or more so than large doses, they suggest certainly that there is no apparent advantage in intravenous therapy over large oral medication in the effect on the P-R interval changes.

DISCUSSION

There is no danger in giving such large doses if the signs of toxicity are known and carefully appraised. Tinnitus and diminished hearing are practically universal with 10 Gm. of sodium salicylate daily and are of no practical significance as far as toxic reactions are concerned. Severe toxic reactions

are marked by hyperpnea, tetany with carpopedal spasm, and progression to maniacal delirium and loss of consciousness. They present a serious situation in the advanced state. Pustular acne is not uncommon with the toxic reaction and is frequently troublesome. It promptly subsides on stopping the drug. The serious toxic reactions in our experience are always preceded by hyperpnea. In this stage reduction of the dose of salicylate or the use of sodium bicarbonate soon relieves the symptoms by reducing the plasma level of the drug. If the drug is continued in the same dosage without sodium bicarbonate, hyperpnea increases and delirium appears. In this stage the use of intravenous saline is necessary to return the body chemistry to normal and relieve the symptoms. We[17] have shown that the chemical changes consist of a respiratory alkalosis with resultant water retention and diminished renal function. It is essential that the premonitory symptoms of severe toxic reactions be well known by those using these large doses of salicylates. In our series of young adults, 20 to 25 grains of sodium salicylate every four hours (six times daily) were usually sufficient to maintain plasma levels of 35 to 50 mg. per 100 cubic centimeters. No sodium bicarbonate was given with this dose and toxic reactions were rarely experienced.

The use of intravenous salicylate is open to considerable question. We were able to maintain more satisfactory plasma levels with oral administration. P. K. Smith[10] has shown that with oral administration the plasma level reaches a peak in one hour. It would appear that intravenous therapy is not necessary. In those patients with heart failure or impending failure, the use of intravenous saline may well be dangerous and may increase the degree of failure. None of our patients receiving intravenous therapy was in cardiac failure and there were no serious reactions. However, nausea and vomiting are very common with intravenous salicylate and in some cases we were forced to discontinue this method of administration because of constant vomiting. After a few hours these patients were able to resume salicylate therapy in large oral doses without difficulty. In our experience intravenous therapy offers no advantage over oral therapy in the control of these patients.

In our group of young adults, the administration of large doses of sodium salicylate was more efficacious than small doses: first, in reducing the febrile response; and, second, in the treatment of acute pericarditis. It did not diminish the period of rheumatic activity as shown by the effect on the sedimentation rate; it did not prevent the occurrence of valvular heart disease; and it did not prevent the progression of polycyclic attacks of rheumatic fever. There may be certain advantages in using large amounts especially at the start of therapy and until the fever and the symptoms have subsided. There seems to be some question as to the necessity for continuing the salicylate after these effects have been achieved. Patients taking large doses have almost constant tinnitus and diminished hearing so that cessation of the drug will make them more comfortable.

It would appear that the use of large amounts of salicylate offers some advantage in the treatment of rheumatic fever. The early reduction of fever and pain would tend to decrease the heart rate and reduce cardiac work. How-

ever, it will not prevent cardiac damage as is shown by the experience of McEachern,[7] Keith and Ross,[11] and ourselves. Moreover, as Swift[3] has pointed out, if in attaining this early relief of symptoms the patient is led to believe he is cured and is allowed to resume normal activity, he may suffer as much or more permanent injury than if he were untreated. It is important to emphasize that sodium salicylate in these doses does not bring about a cure. There is still no chemotherapeutic routine which will obviate the need for prolonged reduction in physical activity as the most important method of treatment in acute rheumatic fever.

CONCLUSIONS

1. The use of sodium salicylate in amounts of 10 to 16 Gm. per day will reduce the temperature more quickly in acute rheumatic fever than will small doses. Likewise large doses appear to offer an advantage in the treatment of acute rheumatic pericarditis.

2. The use of sodium salicylate in doses of 10 to 16 Gm. per day will not prevent the development of cardiac damage or the progression of pre-existing heart disease. Large doses of salicylate will not serve to shorten the period of rheumatic activity anymore than small amounts. Large doses of salicylate will not prevent the development of polycyclic attacks of rheumatic fever.

3. The routine use of sodium salicylate by intravenous infusion is not warranted by the evidence presented to obtain a rapid elevation of the plasma salicylate level, to maintain a high plasma level, or to effect the fever or sedimentation rate.

4. If large amounts of salicylate are given, either orally or intravenously, the premonitory signs of toxicity must be recognized early and the dose must be reduced to prevent progression of the symptoms.

5. It appears that the use of large amounts of salicylate may offer some advantage in the first weeks of therapy and may bring about a rapid reduction of the fever and alleviation of the symptoms; but the continued administration of large amounts of this drug until the sedimentation rate is normal is of questionable value.

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A REFRACTORY CASE OF SUBACUTE BACTERIAL ENDOCARDITIS DUE TO VEILLONELLA GAZOGENES CLINICALLY ARRESTED BY A COMBINATION OF PENICILLIN, SODIUM PARA-AMINOHIPPURATE, AND HEPARIN

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SINCE the value of penicillin alone or with heparin has been established,[1-4] bacterial endocarditis is being studied very intensively. It is not surprising, therefore, that infecting organisms of a bizarre nature are occasionally encountered. A most unique example of a bizarre infecting organism was found in a patient who was admitted to the Jewish Hospital of Brooklyn on April 14, 1944. Before the patient entered our hospital, the organism had been recovered from the blood stream with great difficulty, under the direction of Dr. Gregory Schwartzman, and identified by him and his group as a *Veillonella* species. This same gram-negative anaerobic coccus was isolated by us repeatedly and its biologic characteristics, including its response in the test tube to various anti-infective agents, were studied in great detail. It was considered worth while to report this case (1) because of the unusual nature of the infecting organism, its extreme resistance to penicillin presenting an almost insurmountable obstacle to the successful treatment of the patient, and (2) because of the singular measures employed in overcoming all the difficulties encountered and accomplishing clinical arrest of the infection. The case is further noteworthy because of the huge amounts of penicillin* which were employed, a fact which gives further testimony to the nontoxicity of this agent. Finally, it is the first recorded instance, so far as we know, wherein sodium para-aminohippurate† was used as an indispensable enhancing agent in the actual treatment of a patient infected with a refractory organism.

CASE REPORT

S. Z., a 35-year-old white man, was admitted to the Jewish Hospital of Brooklyn on April 14, 1944, with a history of fever of seven months' duration. The patient's illness began on Sept. 4, 1943, with chills, fever, and pain in the right shoulder. At this time a painless, red spot appeared on the big toe of his right foot. He was admitted to another hospital where a course of atabrine was given without effect. One month later he was transferred to a second hospital where

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†We are indebted to Sharp and Dohme, Inc., for the liberal supplies of sodium para-aminohippurate and to Dr. Karl H. Beyer of that organization for his advice and cooperation.

he was treated with massive doses of the sulfonamide drugs. At the latter institution a gram-negative anaerobic organism was isolated from the blood stream which was identified as *Veillonella* species. There was some symptomatic improvement as a result of the chemotherapy, but, as soon as treatment was stopped, the clinical symptoms recurred. The patient denied having had rheumatic fever.

On admission to our institution, the patient was found to be of athletic habitus. His temperature was 100.4° F., pulse rate, 100; respirations, 24; and blood pressure, 105/65. The heart did not appear to be enlarged, but there was a loud, rough, apical systolic murmur. The spleen was slightly tender and palpable 2 fingerbreadths below the costal margin. There were two red spots on the right thumb. Culture of the blood on admission was sterile. The sedimentation rate was 92 mm. in one hour (Westergren method); hemoglobin, 78 per cent; red blood cells, 4,200,000 per milliliter; white blood cells, 7,100 per milliliter, with 70 per cent polymorphonuclear leucocytes, 26 per cent lymphocytes, and 4 per cent monocytes.

Treatment was begun on April 18, 1944, with penicillin and heparin. The patient was given a two-week course of penicillin and heparin by continuous intravenous drip, totalling 3,430,000 units of penicillin and 900 mg. of heparin. Therapy had to be interrupted on one occasion because of violent pyrogenic reactions in which the temperature reached a height of 107° F.

During treatment, the patient ran a daily remittent temperature up to 104° F. which apparently was uninfluenced by the treatment. On May 5 he was given sulfadiazine in dosages up to 9 Gm. daily. This was continued for a period of ten days and was supplemented with 20,000 units of penicillin every two hours intramuscularly during the last four days of this cycle. Again, little or no success attended this treatment except for the fact that the temperature continued at a slightly lower level. Sulfonamides were therefore discontinued, and the patient was again put on continuous intravenous penicillin therapy receiving 240,000 units daily for six days with no clinical benefit. Penicillin was discontinued on May 19, 1944, and oral sulfadiazine was again resumed. On May 24, the oral chemotherapy was supplemented with intravenously administered sulfadiazine; 20 Gm. of the sodium salt, combined with 30 Gm. of urea, in 1,000 ml. of normal saline was administered daily. This was continued until May 31 and was of no benefit to the patient. On June 1, he was again put on continuous intravenous penicillin, receiving 500,000 units daily. This had to be discontinued after four days because of limited supplies. On June 7, massive intravenous sulfadiazine was again started. He received 20 Gm. of the drug combined with 30 Gm. of urea and 1 Gm. of ascorbic acid in 1,000 ml. of normal saline; but because of the mutilated condition of the patient's veins, therapy had to be suspended the following day. The patient received no therapy at all during the next week and the temperature unaccountably declined gradually and reached normal on June 14. On this date, for the first time since admission, culture of the blood yielded a gram-negative anaerobic organism, *Veillonella* species. The organism was thereafter repeatedly recovered from the blood stream until the

infection was apparently arrested. On June 21, the patient was again started on massive cyclic intravenous sulfonamide therapy. He was given 20 Gm. of sulfadiazine plus 30 Gm. of urea and 1 Gm. of ascorbic acid dissolved in 1 liter of distilled water on two successive days each week for the next four weeks. The patient's condition, however, did not improve, and consequently penicillin-heparin was again started on July 14. A fourteen-day course of treatment was given, with daily dosage of one million units of penicillin plus 100 mg. of heparin in 1 liter of solute. Although the temperature curve remained relatively flat during treatment, as soon as it was suspended, the daily, swinging character, with spikes up to 103° F., was resumed (Fig. 1). A blood culture taken during treatment was negative, but one repeated the day treatment was stopped was positive.

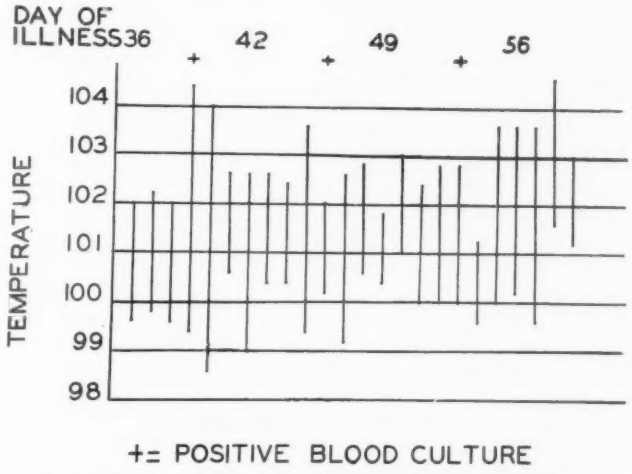

Fig. 1.—Graph showing typical daily fluctuations in temperature while patient was clinically and bacteriologically active.

The patient's veins were in such poor condition that it was necessary to defer penicillin therapy until August 9, when it was again administered under the same dosage plan. Treatment was continued for nine days, when available veins gave out. During this span of treatment the temperature continued its remittent course, but the daily peaks were on a lower level, i.e., up to 101° F.

In view of the ineffectiveness of treatment up to this point, all therapy was now interrupted and the patient was investigated for possible extracardiac foci of infection. Several devitalized teeth were found and these were surgically removed on Sept. 19, 1944. The patient withstood the procedure well, but his clinical course indicated continued bacterial activity. A blood culture taken on September 25 was again positive.

Up to this date, the patient had been in the hospital for about five and one-half months and had received a total of almost 31 million units of penicillin. Although the endocarditis remained active, his general status was surprisingly good. It was felt that, if nothing else, treatment had succeeded in maintaining a status quo and that, ultimately, persistence and revised dosage schedules would meet with success.

Between September 25 and October 30 the patient was given another course of penicillin. The basic dosage plan was now 2 million units daily. During portions of this course the diluent used was 1,000 ml. of sodium para-aminohippurate in 4 to 8 per cent concentration. Treatment under this plan was entirely probatory and had to be interrupted on several occasions because of complicating local thrombophlebitic reactions. In all, he received 45 million units of penicillin, but, at the end of this span, the temperature curve reflected clinical activity although blood cultures were sterile.

On November 6, an eighteen-day course of treatment was begun. The treatment plan at this time called for 2 million units of penicillin daily dissolved in 1,000 ml. of 4 per cent sodium para-aminohippuric acid. When treatment was discontinued on November 24, there had been absolutely no change in the temperature curve. A blood culture taken on November 28 was positive. About the most that could be said at this juncture was that there still had been no deterioration in the patient's general condition.

Obviously, with so much intravenous work having been done, the patient's veins were seriously compromised. It was therefore necessary to defer further therapy until December 11. At this time the daily dosage plan for penicillin was revised to 5 million units, and, in order to conserve the veins, it was dissolved in 500 ml. normal saline and given by continuous intramuscular drip. Treatment by this route proved extremely painful and distressing and had to be suspended four days later, after a total of 20 million units had been administered.

Continuous intravenous medication was again resumed on December 19; the daily dosage plan at this time varied from 2 to 5 million units of penicillin plus 200 mg. of heparin dissolved in 1,000 ml. of normal saline. At times, the diluent used was 8 per cent sodium para-aminohippurate so that blood assays for penicillin with and without the supplemental use of this drug could be done. Treatment was continued for thirty-one days and was stopped on Jan. 19, 1945; a total of 131 million units of penicillin had been given. During much of this course, the temperature receded and remained flat. This was most encouraging in view of the fact that blood cultures were also negative. However, on January 24, the patient had a chill and the temperature again began its daily remittent course with peaks up to 103° F.

As a result of the encouraging response observed during the previous span of treatment, another course was projected with increasing dosage of penicillin up to 10 million units daily, combined with heparin. The basal daily dosage for a good portion of this period was 5 million units. Treatment was begun on January 31, and continued for thirty-seven days, ending on March 8, 1945; a total of 173 million units of penicillin were given. The general condition of the patient remained in statu quo during this treatment. The temperature curve became irregularly lower and the cycle was finally interrupted because of the apparent futility of the treatment program and the fact that the patient's veins again were badly mutilated.

Probationary in vitro tests had indicated the effectiveness of streptomycin. Pending the acquisition of adequate amounts of this antibiotic and in order to

allow both the patient's morale and his veins to recover, he was sent home and given a respite from hospital routine.

Up to this time, the patient had been in the hospital almost a full year and had received a total of about 467 million units of penicillin. Despite the fact that his endocarditis was clinically and bacteriologically still active, his general condition was quite favorable. There had been no embolic complications.

During the month the patient was at home the organism was again subjected to intensive study. It was finally identified as *Veillonella gazogenes*. Inasmuch as there was unexpected delay in obtaining streptomycin, the organism was retested against penicillin. In vitro tests showed bacteriostasis at 10 units of penicillin per milliliter. However, 30 units of penicillin per milliliter were required for a complete bactericidal effect. It was apparent that the previous dosage schedules had been inadequate, since blood assays had never reached appropriate therapeutic levels. Since our studies[5] had shown that we could expect serum penicillin levels of approximately 1 unit per milliliter for each million units of penicillin administered daily, it was obvious that the requisite dosage schedule called for at least 30 million units per day. While it was theoretically possible to administer this huge daily dosage of penicillin it was felt that further experimentation with the use of para-aminohippuric acid as an enhancing agent was indicated. These experiments (Tables I and II) were accordingly carried out during the first few weeks following the patient's readmission to the hospital on April 9, 1945.

On his return to the hospital, it was evident that the patient's general condition had not deteriorated. He was febrile and two blood cultures taken on April 5 (at home) and April 10 revealed numerous colonies of *Veillonella gazogenes*. Probatory experiments with various dosage schedules of penicillin together with para-aminohippuric acid (Table II) led us to assume that adequate therapeutic levels could be consistently maintained if the following program was followed: (1) minimum daily dosages of 10 million units of penicillin, (2) minimum daily dosage of 240 Gm. of sodium para-aminohippurate.

The patient was accordingly started on his new treatment program on May 11, 1945. He was given, daily, 10 million units of penicillin dissolved in 2 liters of 12 per cent sodium para-aminohippuric acid solution to which were added 50 mg. of heparin. This modest amount of heparin, by preventing regional thrombophlebitis, has been found effective generally in the face of huge penicillin dosage. Over a period of sixteen days (Figs. 2 and 3), he received the equivalent of thirteen full days of treatment, or 130 million units of penicillin. The results were prompt and dramatic. Within three days after the program was initiated, the temperature became normal and has remained so far almost six months. As a prophylactic measure, the remainder of his potentially infected teeth were surgically removed. The patient was discharged from the hospital on June 23, 1945, clinically well.

At the time of discharge the patient weighed 190 pounds (86 kg.) as contrasted with a low of 166 pounds (75 kg.) on April 10, 1945. The spleen, which had previously been consistently palpable, receded promptly. The sedimentation rate

was 12 mm. in one hour as compared with a high of 95 mm. on May 5, 1944. The blood picture showed hemoglobin, 90 per cent; red blood cells, 4,660,000; white blood cells, 6,850, with a differential of 55 per cent polymorphonuclear

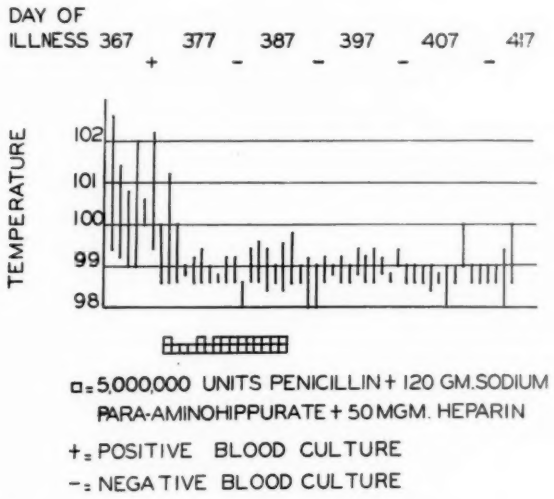

Fig. 2.—Graph showing response of patient to curative cycle of therapy.

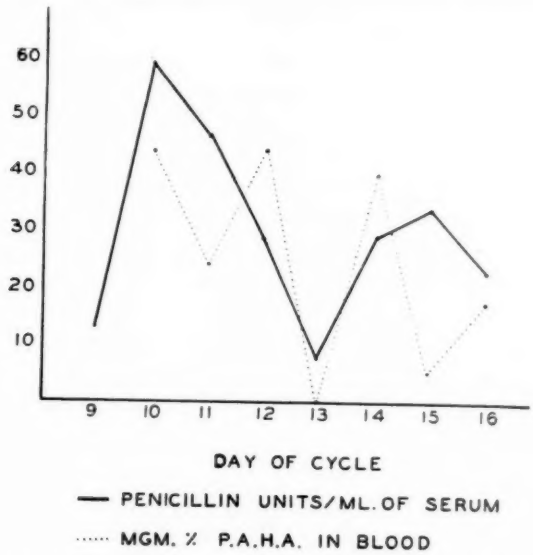

Fig. 3.—Graph showing actual blood assays of penicillin and para-aminohippuric acid during curative cycle of therapy.

leucocytes, 44 per cent lymphocytes, and 1 per cent eosinophiles. Previously, there had been a peristent secondary anemia which was controlled only by repeated transfusions of whole blood. The albumin and erythrocytes found in

the urine during the active phases of the disease disappeared with termination of the infection. The patient has been seen at intervals since his discharge. His condition is excellent, and cultures of the blood have been consistently sterile.

EXPERIMENTAL STUDIES

Blood cultures were taken in 0.1 per cent brain-heart infusion agar broth (Difco) and 0.1 per cent Savita glucose agar broth, to both of which was added 0.1 per cent agar. The cultures were incubated for four to seven ways at 37° C. and then surface plated on blood agar by inoculating the plates with the incubated blood broth culture. The transplanted cultures were placed in a candle jar (10 per cent carbon dioxide) and kept for three days at 37° C. Colonies were picked from these plates, transferred, and identified. After repeated transfers, the use of a candle jar could be dispensed with and the organism could be grown sluggishly at room temperature. The organism was identified as *Veillonella gazogenes*, which, according to Bergey,[6] is prevalent in the saliva of man and other animals. Although it was not possible to isolate the organism from the patient's mouth or from his tooth sockets and roots, the portal of entry may nevertheless well have been the oral cavity.

As indicated in the clinical review, the organism was extremely resistant to daily dosages of penicillin per se up to and including 10 million units. In vitro titrations of suspensions of the organism against varying concentrations of penicillin showed bacteriostasis at 10 units of penicillin per milliliter. A complete bactericidal effect was not obtained until the concentration of 30 units of penicillin per milliliter was reached. Although streptomycin was not available for clinical use, it was possible to obtain some for in vitro experimental purposes. It was found that the inhibiting concentration of streptomycin was 10 units per milliliter.

It was necessary to evaluate dosage schedules of the chemotherapeutic agents in the light of these facts. Previous studies[5] had indicated that with a given dosage schedule of penicillin administered by the continuous intravenous route, expected sustained serum assays approached 0.1 unit per 100,000 units daily. In other words, in order to attain bactericidal serum penicillin levels in this patient, the daily dosage theoretically would have had to be at least 30 million units.

Because variations in blood levels exist in the individual case, an experiment was designed to see what levels could be obtained in this patient with varying dosages of penicillin. Equivalent dosages of penicillin were calculated and dissolved in 166 ml. of normal saline to cover an experimental period of two hours for each dose. The patient was carefully observed throughout so that the prescribed amounts of penicillin were infused. Blood was drawn at the end of each hour and serum penicillin assays were performed according to the method of Rosenblatt, Alture-Werber, Kashdan, and Loewe.[7] Table I indicates the serum penicillin levels obtained with equivalent daily dosages up to 30 million units per day.

TABLE I. SERUM PENICILLIN LEVELS WITH VARYING DOSAGE OF PENICILLIN

PENICILLIN* UNITS/HR. (× 1,000)	EQUIVALENT DAILY DOSAGE (× 1,000)	SERUM PENICILLIN UNITS/ML.				
		1 HOUR	2 HOURS	AVERAGE	THEORETICAL†	DEVIATION
415	9,960	3.33	12.0	7.67	9.96	− 2.29
457.5	10,980	8.57	8.57	8.57	10.98	− 2.41
500	12,000	15.0	12.0	13.5	12.0	+ 1.5
541.5	12,966	15.0	15.0	15.0	12.9	+ 2.1
582.5	13,980	7.5	15.0	11.25	13.98	− 2.74
625	15,000	15.0	15.0	15.0	15.0	0.0
667.5	16,020	24.0	15.0	19.5	16.0	+ 3.5
						Total − 7.44
						+ 7.1
710	17,040	20.0	20.0	20.0	17.0	+ 3.0
750	18,000	12.0	15.0	13.5	18.0	− 4.5
792.5	19,020	15.0	30.0	22.5	19.0	+ 3.5
835	20,040	30.0	24.0	27.0	20.0	+ 7.0
875	21,000	15.0	30.0	22.5	21.0	+ 1.5
918	22,020	30.0	30.0	30.0	22.0	+ 8.0
960	23,040	30.0	30.0	30.0	23.0	+ 7.0
1,000	24,000	17.1	20.0	18.56	24.0	− 5.44
1,042.5	25,020	24.0	30.0	27.0	25.0	− 2.0
1,085	26,040	30.0	40.0	35.0	26.0	+ 9.0
1,127.5	27,060	30.0	——	30.0	27.0	+ 3.0
1,170	28,080	15.0	20.0	17.5	28.0	− 9.5
1,210	29,100	48.0	40.0	44.0	29.1	+14.9
1,260	30,220	60.0	40.0	50.0	39.2	+10.8
						Total −21.44
						+67.7

*Diluent was 83 ml. of normal saline per hour. This is equivalent to approximately 1,000 ml. per day.

†This is based upon expected serum penicillin level of 0.1 unit per daily dosage of 100,000 units.

It is seen that with dosages up to 15 million units per day the actual figures obtained were fairly close to theoretically expected values. With dosages above 15 million units daily, most of the actual serum assays tended to be higher than the theoretical. This may possibly be due to the fact that the point of maximal renal clearance for penicillin had been exceeded. This problem, however, is being further investigated.

According to this study, daily dosage of 20 million units of penicillin or more might consistently yield the requisite bactericidal level of 30 units per milliliter of serum. It was felt that a saving of penicillin could be effected through the concurrent use of sodium para-aminohippurate, which Beyer and his co-workers[8] had proposed as an agent for aiding the economy with which the body utilizes penicillin.

Our previously published studies[9] confirmed Beyer's observations, but it was found necessary to administer at least 200 Gm. of sodium para-aminohippurate daily in order to attain blood concentrations sufficient to augment serum penicillin levels appreciably. In order to administer this amount of the

TABLE II. AUGMENTATION OF SERUM PENICILLIN LEVELS BY SIMULTANEOUS ADMINISTRATION OF PARA-AMINOHIPPURIC ACID

HR.	PENICILLIN* UNITS/HR.	EQUIVALENT DAILY DOSAGE	SODIUM PARA-AMINOHIPPURATE†	BLOOD SERUM PENICILLIN UNITS/ML.	ASSAY P. A. H.‡ MG.%
1	417,500	10,020,000	0	7.5	—
2			0	7.5	—
3			12 per cent Sodium P.A.H. and priming doses of 50 c.c. 20 per cent solution at three and five hours	15.0	39.7
4				15.0	27.6
5				15.0	59.6
6				15.0	47.5
7			0	15.0	24.2
8			0	15.0	10.2
1	625,000	15,000,000	0	12.0	—
2			0	13.2	—
3			12 per cent Sodium P.A.H. and priming doses of 50 c.c. 20 per cent solution at three and five hours	20.0	34.1
4				30.0	35.0
5				30.0	51.8
6				30.0	60.5
7			0	30.0	26.6
8			0	30.0	12.3
1	832,500	19,980,000	0	15.0	—
2			0	15.0	—
3			12 per cent Sodium P.A.H. and priming doses of 50 c.c. 20 per cent solution at three and five hours	30.0	29.4
4				40.0	32.8
5				40.0	61.3
6				48.0	60.5
7			0	48.0	31.5
8			0	40.0	12.9

*During control run of two hours (see text), the diluent for penicillin was 166 ml. of normal saline. This is equivalent to a daily intravenous of approximately 2,000 milliliters.

†During sodium para-aminohippurate run of four hours the diluent for penicillin was 333 ml. of 12 per cent sodium para-aminohippurate in distilled water. This is equivalent to 2 liters daily, or 240 Gm. of the drug. The actual amount given during the four-hour period was 48 grams.

‡P. A. H.=Sodium para-aminohippurate.

enhancing agent effectually, the total daily volume of fluid given intravenously had to be increased from 1 to 2 liters, since a 20 per cent concentration of sodium para-aminohippurate was found to be too irritating for continuous venoclysis. A 12 per cent concentraton of the drug (120 Gm. per liter) was satisfactory for maintenance purposes.

Table II summarizes an experiment designed to test the enhancing effect of para-aminohippuric acid. Study of the table shows consistent augmentation of the serum penicillin levels by the simultaneous administration of sodium para-aminohippurate. Although the short-term experiment indicated that a minimum daily dosage of 15 million units of penicillin together with para-aminohippurate might be required for optimum results, it was felt that under actual clinical conditions, there might be a cumulative effect of the antibiotic with smaller dosage. It was decided, therefore, that the projected therapeutic course should encompass the simultaneous, continuous administration of 10 million units of penicillin daily dissolved in 2 liters of 12 per cent sodium para-aminohippurate in distilled water. Heparin was added in order to maintain a continuous intravenous flow and make possible an uninterrupted span of treatment.

Fig. 3 indicates the actual serum penicillin and para-aminohippuric acid levels obtained during this span of treatment. The determinations were taken usually at the end of a day's run, prior to attaching a fresh bottle of soluton. It is observed that most of the penicillin levels are within or above the desired effective therapeutic zone. The fact that this course of treatment resulted in the apparent clinical arrest of the disease process is confirmation of the validity of the experimental approach.

As a corollary to what has been presented, it was necessary to ascertain the effect, if any, of sodium para-aminohippurate upon the infecting organism. Titrations were therefore carried out in brain-heart infusion broth, and the results are summarized in Table III.

TABLE III. TABLE SHOWING RESISTANCE OF VEILLONELLA GAZOGENES TO THERAPEUTIC AGENTS

DRUG	BACTERIOSTASIS	MINIMUM LETHAL DOSE
Penicillin	10 Oxford units per milliliter	30 Oxford units per milliliter
Penicillin plus P. A. H.,* 20 mg.%	10 Oxford units per milliliter	30 Oxford units per milliliter
Penicillin plus P. A. H., 30 mg.%	10 Oxford units per milliliter	26 Oxford units per milliliter
Penicillin plus P. A. H., 40 mg.%	10 Oxford units per milliliter	20 Oxford units per milliliter
Penicillin plus P. A. H., 50 mg.%	10 Oxford units per milliliter	15 Oxford units per milliliter
P. A. H	40 mg. per cent	163 mg. per cent
P. A. H. plus penicillin, 10 units/ml.	16 mg. per cent	63 mg. per cent
Streptomycin	10 units per milliliter	10 units per milliliter

*P. A. H. = Sodium para-aminohippurate.

It was noted that sodium para-aminohippurate itself is bacteriostatic at a concentration of 40 mg. per cent and bactericidal at 160 mg. per cent. With a standard level of 10 units of penicillin per milliliter in brain-heart infusion broth, a synergistic effect was observed when varying concentrations of sodium para-aminohippurate were added. The bacteriostatic and minimal lethal zones of sodium para-aminohippurate were reduced to 16 mg. per cent and 63 mg. per cent, respectively, in the presence of 10 units of penicillin per milliliter of test broth.

The converse of what has been discussed is also summarized in Table III. To brain-heart infusion broth containing 20 to 50 mg. per cent of sodium para-aminohippurate were added varying concentrations of penicillin. These were inoculated with *Veillonella gazogenes* and incubated for twenty-four hours. At a concentration of 50 mg. per cent of sodium para-aminohippurate the bacteriostatic level of penicillin remained at 10 units per milliliter in all instances, but the bactericidal zone was progressively reduced until it reached 15 units of penicillin per milliliter, almost approximating the bacteriostatic level.

These experiments indicate a pronounced synergistic effect between penicillin and sodium para-aminohippurate. Thus, consistent minimal lethal levels against the infecting organism in this case could obviously be reached more readily with the conjoint use of both drugs than could have been achieved by the use of either one, per se.

SUMMARY AND CONCLUSIONS

1. A unique case of subacute bacterial endocarditis due to *Veillonella gazogenes* has been presented.

2. Massive sulfonamide therapy was ineffectual in terminating the infection.

3. Twelve courses of penicillin therapy of varying length, combined at times with adjuvants such as sulfonamides and heparin, failed to sterilize the blood stream although progress of the infection was retarded during the year of this treatment. Dosages of penicillin up to 10 million units per day by the continuous intravenous route were nontoxic and well tolerated. A total of 466,670,000 units of penicillin was used during this period.

4. In vitro studies revealed bacteriostasis for the organism at 10 units per milliliter of streptomycin and penicillin. The minimum lethal dose was 10 units per milliliter and 30 units per milliliter for streptomycin and penicillin, respectively.

5. With a constant concentration of 10 units per milliliter of penicillin, the bacteriostatic and minimum lethal dose of sodium para-aminohippurate was 16 mg. per cent and 63 mg. per cent, respectively. This contrasts with bacteriostatic and lethal doses of 40 mg. per cent and 163 mg. per cent, respectively, of sodium para-aminohippurate, per se.

6. With concentrations of sodium para-aminohippurate varying from 20 to 50 mg. per cent, the minimum lethal dose of penicillin against the infecting organism was lowered as much as 15 units per milliliter.

7. These data were clinically applied with satisfactory results by the simultaneous daily intravenous administration of penicillin and sodium para-aminohippurate in doses of 10 million units and 240 Gm., respectively, over a period of sixteen days. Heparin was also incorporated for its beneficial effect in maintaining an uninterrupted venoclysis.

8. This is the first case in which sodium para-aminohippurate has been used with penicillin in the actual clinical arrest of an infection otherwise highly resistant to the action of penicillin alone.

9. The case demonstrates the need for close collaboration between the laboratory and the clinician for optimum results.

The authors desire to express their appreciation of the contributions made by Miss M. Kozak, Mr. M. Russell, and Miss F. Kashdan.

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CARDIAC OUTPUT IN HEART FAILURE

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SINCE the pioneer work of von Plesch in 1909,[1] extensive research has been done on the behavior of cardiac output in valvular, hypertensive, and coronary heart diseases. Von Plesch, like most of his followers,[2-45] found great variability in the cardiac output of cardiac patients with or without failure. Their results are likely to be criticized because of the methods used or because basal conditions were not accurately observed. In general, however, their results showed normal or diminished cardiac output.

Starr and his associates,[46-48] using the ethyl iodide method modified by Starr and Gamble,[49] observed that generally the cardiac output was normal in compensated cardiac patients. In patients with failure they usually found a diminished cardiac output, though in some the values were within normal range. They failed to find a correlation between cardiac output and functional capacity of the heart. Altschule and Blumgart,[50] using the same method as Starr and his associates, observed that the cardiac output was at the lower limit of normal in a patient with mitral, tricuspid, and aortic stenosis and insufficiency.

Grollman and his co-workers[51] investigated the possible application of the acetylene technique in cardiac patients, showing that it was desirable to take at least three samples during the rebreathing period. In their small series of patients with severe heart failure, the cardiac output was diminished in some and within the normal range in others. Using the same method, McMichael[52] showed that the cardiac output was normal in compensated cardiac patients and diminished in those with failure, but no consistent correlation could be demonstrated between the degree of the insufficiency and the cardiac output. Taquini and his co-workers,[53] using the acetylene technique with three or four samples, studied a series of patients with mitral stenosis, either compensated or with a mild degree of failure. In their cases the figures for the average cardiac index were lower than those for the normal controls, both in patients with normal sinus rhythm and in those with auricular fibrillation.

Some investigators were especially interested in finding a correlation between the severity of heart failure and cardiac output. Harrison and his associates[54] and Harrison,[55] using the acetylene method (three or four samples), found that in general the cardiac output was diminished in patients with cardiac failure. They concluded, however, that there was no relation between the degree of the

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insufficiency and the cardiac output or the arteriovenous oxygen difference. In support of this conclusion they pointed out that, in the same patient, a clinical improvement can be associated with increased, diminished, or no change in cardiac output and arteriovenous oxygen difference.

McGuire, Hauenstein, and Shore,[56] using the acetylene and the direct Fick method on a small number of patients, could not find a consistent correlation between the degree of heart failure and the diminution of cardiac output. Later,[57-59] using the three-sample acetylene method on a greater number of cases of congestive heart failure, they observed that, as the insufficiency was more severe, the cardiac index was reduced further, with only a few exceptions which could be readily explained on the basis of such extracardiac factors as metabolism, venous pressure, hyperpnea, and so forth. They divided the patients into four groups according to the severity of the congestive heart failure, noting that the difference in cardiac index of any two consecutive groups was not statistically significant although it was significant between the first and the last group.

Stewart and co-workers[60, 61] pointed out that a close correlation could be drawn between the clinical condition and the cardiac output in rheumatic, hypertensive, arteriosclerotic, and syphilitic heart disease. Using the three-sample acetylene method, they showed that the average cardiac index was slightly reduced in patients who never had experienced cardiac insufficiency, and that it was much lower in cases with congestive heart failure. In a group of patients studied after recovery from failure, the figures for the average cardiac index showed a value between those of the patients with compensated heart disease and those of the patients with congestive failure. The clinical improvement was accompanied by an increase of the cardiac output although the values of the first group were not reached. These results led Stewart and his co-workers to the conclusion that there is an inverse correlation between the degree of heart failure and the cardiac index.

Stewart and his co-workers[60] found that "single lesions are not incompatible with a fairly normal circulation at rest, but in all instances in which there is more than one lesion functional alterations appear." They held also that aortic stenosis combined with other valvular lesions resulted in marked decrease in function. On the other hand, aortic regurgitation seemed to be of functional benefit when superimposed on mitral stenosis and insufficiency and resulted in less impairment of the circulation than was found in mitral stenosis and insufficiency alone. The same authors said, "The order of magnitude of the functional defect increased progressively in going from the mitral stenosis and insufficiency, aortic insufficiency group, to the mitral stenosis and insufficiency group, to the mitral stenosis and insufficiency, aortic stenosis and insufficiency group."

MATERIAL AND METHODS

A total of seventy-five determinations were made in forty-two patients. They were grouped under the following diagnoses:

DIAGNOSIS	NUMBER OF PATIENTS	NUMBER OF DETERMINATIONS
Mitral stenosis and insufficiency, sinus rhythm	13	23
Mitral stenosis and insufficiency, auricular fibrillation	9	20
Mitral stenosis and insufficiency, aortic insufficiency	1	1
Mitral stenosis and insufficiency, tricuspid stenosis and insufficiency	2	2
Mitral stenosis, interauricular septal defect	3	5
Aortic insufficiency	2	3
Aortic stenosis and insufficiency	2	5
Hypertensive and coronary heart disease	10	16
Total	42	75

The patients were classified according to their functional capacity at the moment of the determinations, whether they were being treated or not, following the criteria and nomenclature of the New York Heart Association.[63] Our results in a group of seventeen normal subjects were used as controls.

The oxygen consumption was determined by an open circuit method using a Tissot spirometer; the air was collected in ten-minute periods. The arteriovenous oxygen difference was determined with the acetylene method of Grollman[62]; four samples were taken during the rebreathing period. The gas analyses were carried out in the Haldane apparatus with a device for the absorption of the acetylene, and a 12 c.c. burette was used. All the determinations were carried out under basal conditions with the patient sitting in a comfortable armchair at an angle of 105 degrees and with the knees flexed. In every case the patient had been trained to carry out the procedure beforehand.

A statistical evaluation of the results was carried out using the following equations: standard deviation $= \sigma = \sqrt{\frac{\Sigma d^2}{(n-1)}}$; and standard error $= \epsilon = \sqrt{\frac{\Sigma d^2}{n(n-1)}}$. In groups of less than ten cases the following equations were applied: standard deviation $= \sigma = \sqrt{\frac{\Sigma d^2}{(n-3)}}$; and standard error $= \epsilon = \sqrt{\frac{\Sigma d^2}{n(n-3)}}$. Comparing the different groups, the standard deviation of the difference between the averages was calculated according to the equation $\sqrt{E^2_{I} + E^2_{II}}$. The differences were considered statistically significant when they were equal to or greater than three times their standard deviation and very probably real when they fell between two and three times their standard deviation.

RESULTS

In Tables I to V are summarized the results of all the determinations. The average values in each group with the various lesions follow:

Mitral Stenosis and Insufficiency, Sinus Rhythm.

Cardiac Index: Class I, 2.27 liters per square meter per minute (four patients). Class II, 1.99 (six patients). Class III, 1.79 (four patients).

Arteriovenous Oxygen Difference: Class I, 65.5 c.c. per liter of blood. Class II, 66.3. Class III, 80.1.

Heart Rate: Class I, 68 per minute. Class II, 69. Class III, 88.

Systolic Output per Square Meter: Class I, 34.1 c.c. per square meter of body surface. Class II, 29.9. Class III, 20.4.

Mitral Stenosis and Insufficiency, Auricular Fibrillation.

Cardiac Index: Class II, 1.99 liters per square meter per minute (nine patients). Class III, 1.28 (1 patient).

Arteriovenous Oxygen Difference: Class II, 70.7 c.c. per liter of blood. Class III, 110.6.

Heart Rate: Class II, 72 per minute. Class III, 78.

Systolic Output per Square Meter: Class II, 28.3 c.c. per square meter of body surface. Class III, 16.5.

Mitral Stenosis and Insufficiency, Aortic Insufficiency.

Cardiac Index: Class II, 2.02 liters per square meter per minute (one patient).

Arteriovenous Oxygen Difference: Class II, 65.6 c.c. per liter of blood.

Heart Rate: Class II, 73 per minute.

Systolic Output per Square Meter: Class II, 27.5 c.c. per square meter of body surface.

Mitral Stenosis and Insufficiency, Tricuspid Stenosis and Insufficiency.

Cardiac Index: Class II, 1.95 liters per square meter per minute (one patient). Class IV, 1.56 (one patient).

Arteriovenous Oxygen Difference: Class II, 74.0 c.c. per liter of blood. Class IV, 97.4.

Heart Rate: Class II, 82 per minute. Class IV, 98.

Systolic Output per Square Meter: Class II, 23.7 c.c. per square meter of body surface. Class IV, 15.9.

Mitral Stenosis and Insufficiency, Interauricular Septal Defect.

Cardiac Index: Class II, 2.31 liters per square meter per minute (two patients). Class III, 1.57 (one patient).

Arteriovenous Oxygen Difference: Class II, 59.7 c.c. per liter of blood. Class III, 88.0.

Heart Rate: Class II, 59 per minute. Class III, 70.

Systolic Output per Square Meter: Class II, 39.1 c.c. per square meter of body surface. Class III, 22.2.

Aortic Insufficiency.

Cardiac Index: Class I, 2.94 liters per square meter per minute (one patient). Class III, 2.27 (one patient).

Arteriovenous Oxygen Difference: Class I, 53.3 c.c. per liter of blood. Class III, 68.1.

Heart Rate: Class I, 76 per minute. Class III, 70.

Systolic Output per Square Meter: Class I, 38.8 c.c. per square meter of body surface. Class III, 32.3.

Aortic Stenosis and Insufficiency.

Cardiac Index: Class II, 2.02 liters per square meter per minute (one patient). Class III, 1.68 (one patient).

Arteriovenous Oxygen Difference: Class II, 61.6 c.c. per liter of blood. Class III, 86.8.

Heart Rate: Class II, 74 per minute. Class III, 67.

Systolic Output per Square Meter: Class II, 27.2 c.c. per square meter of body surface.

Hypertensive and Coronary Heart Disease.

Cardiac Index: Class I, 2.66 liters per square meter per minute (one patient). Class II, 2.11 (three patients). Class III, 1.82 (five patients). Class IV, 1.60 (two patients).

Arteriovenous Oxygen Difference: Class I, 49.4 c.c. per liter of blood. Class II, 61.5. Class III, 73.3. Class IV, 88.9.

Heart Rate: Class I, 73 per minute. Class II, 63. Class III, 72. Class IV, 77.

Systolic Output per Square Meter: Class I, 36.4 c.c. per square meter of body surface. Class II, 33.7. Class III, 26.0. Class IV, 21.0.

In the calculation of these results, the various determinations on the same individual were averaged, provided that the functional capacity had not changed. In the few cases in which a change was observed in the functional capacity, the results obtained in each case were considered separately within the corresponding capacity group.

With few exceptions, which will be discussed later, the data show that the average values of the patients with different lesions are similar provided the functional capacity is the same. Fig. 1, where the average cardiac index of the

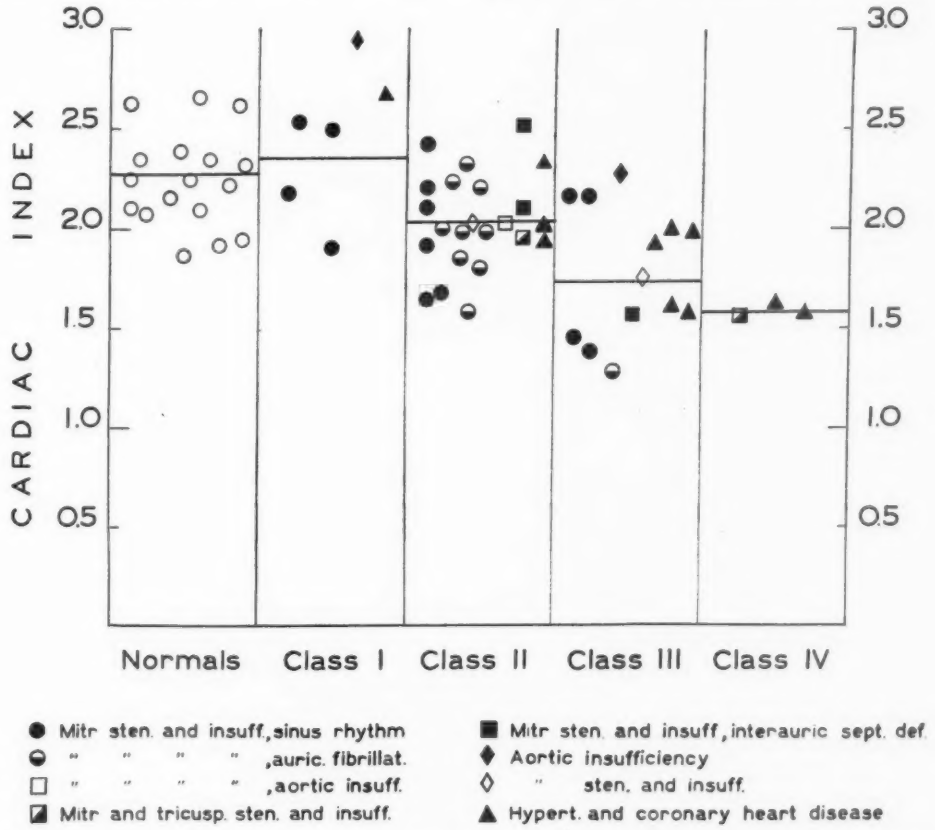

Fig. 1.—Cardiac index of normal patients and those with heart disease. Each symbol represents the average cardiac index of each case. The horizontal lines represent the average cardiac index of all the cases of each group (aortic insufficiency was not included).

TABLE I. MITRAL STENOSIS AND INSUFFICIENCY, SINUS RHYTHM

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O_2 DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	$M.^2$			PER MIN.	C.C. PER MIN.	%	C.C. PER LITER	LITERS PER MIN.	$1/M.^2$ PER MIN.	C.C.	$C.C./M.^2$
1	M	24	1.75	30/ 7/42	Class I Without treatment	83	287	+20.0	79.3	3.62	2.07	43	24.5
C. T.				31/ 7/42	Class I Without treatment	82	292	+22.2	73.1	3.99	2.28	48	27.4
2	M	19	1.92	20/11/42	Class I Without treatment	72	245	− 9.9	65.4	3.75	1.95	52	27.0
D. C.				21/11/42	Class I Without treatment	48	252	− 7.3	71.4	3.53	1.84	73	37.8
3	F	31	1.47	1/ 7/43	Class I Without treatment	60	218	+17.5	57.4	3.80	2.58	63	42.8
M. de M.				2/ 7/43	Class I Without treatment	76	208	+12.3	57.0	3.65	2.48	48	32.6
4	M	33	2.00	31/ 7/44	Class I Without treatment	58	291	+ 6.6	58.0	5.02	2.51	85	42.5
M. M.				11/10/44	Class I Without treatment	64	310	+13.6	62.7	4.95	2.47	77	38.5
5	F	36	1.67	20/ 8/41	Class II Without treatment	77	245	+16.4	66.6	3.68	2.20	48	28.7
R. de G.													
6	F	43	1.81	28/ 7/41	Class II Without treatment	68	197	−12.5	66.2	2.97	1.64	43	23.7
M. de O.													
7	F	41	1.51	10/11/42	Class II Without treatment	78	200	+ 5.0	52.6	3.80	2.52	49	32.3
A. de B.				13/11/42	Class II Without treatment	78	191	+ 1.6	54.6	3.50	2.32	45	29.7
8	M	35	1.70	4/ 5/42	Class II On digitalis and quinidine	62	235	+ 1.2	64.7	3.63	2.13	59	34.5
J. L.				6/ 5/42	Class II On digitalis and quinidine	60	255	+ 9.6	72.2	3.53	2.08	59	34.5
9	F	38	1.52	23/ 4/42	Class II On digitalis	68	193	+ 0.8	69.6	2.77	1.82	41	26.8
A. de S.				24/ 4/42	Class II On digitalis	62	175	− 8.5	57.2	3.06	2.01	49	32.5
10	M	24	1.58	12/11/41	Class III Without treatment	74	188	−12.5	82.0	2.30	1.45	33	20.9
A. C.				27/ 4/42	Class II Off digitalis for three days	60	221	+ 2.5	77.4	2.85	1.80	47	30.1
				5/ 5/42	Class II Off digitalis for eleven days	70	204	− 5.6	82.3	2.48	1.57	35	22.1
11	M	16	1.56	7/ 5/41	Class III Without treatment	107	250	0	74.0	3.37	2.16	31	19.9
J. A.													
12	F	28	1.69	29/ 7/42	Class III On digitalis	100	245	+13.5	66.9	3.66	2.16	37	22.1
S. de. C.													
13	F	54	1.55	8/11/44	Class III Without treatment	70	211	+12.5	96.6	2.18	1.41	31	20.1
M. de V.				10/11/44	Class III Without treatment	77	210	+12.2	99.3	2.10	1.35	27	17.6

TABLE II. MITRAL STENOSIS AND INSUFFICIENCY, AURICULAR FIBRILLATION

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O_2 DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	M.²			PER MIN.	C.C. PER MIN.	%	C.C. PER LITER	LITERS PER MIN.	1/M.² PER MIN.	C.C.	C.C./M.²
14	F	17	1.65	16/ 4/42	Class II On digitalis	85	237	+ 3.7	77.0	3.07	1.86	36	21.8
C. V.				21/ 4/42	Class II On digitalis	70	216	− 5.2	71.0	3.04	1.85	43	26.1
				28/ 4/42	Class II On digitalis	64	218	− 3.3	71.1	3.06	1.85	48	29.1
15	M	34	2.05	18/ 6/41	Class II On digitalis	95	356	+26.8	82.1	4.33	2.11	45	22.0
R. C.				23/ 6/41	Class II On digitalis	90	355	+26.7	75.0	4.73	2.30	52	25.4
				27/ 6/41	Class II On digitalis	90	365	+30.5	72.0	5.07	2.47	56	27.3
			2.06	5/12/41	Class II Without treatment	90	297	+ 6.3	74.9	3.96	1.92	44	21.5
			2.05	15/12/41	Class II On digitalis	72	270	− 3.8	55.5	4.86	2.35	67	32.7
16	F	44	1.51	10/ 4/42	Class II On digitalis	65	210	+11.6	78.0	2.69	1.78	41	27.2
C. de L.				13/ 4/42	Class II On digitalis	60	201	+ 6.9	68.3	2.94	1.94	49	32.5
				14/ 4/42	Class II On digitalis	62	196	+ 4.1	77.0	2.55	1.68	41	27.2
17	M	25	1.67	8/ 8/41	Class II On digitalis	60	222	− 2.5	57.2	3.88	2.32	65	38.9
G. C.													
18	F	39	1.91	22/ 8/42	Class II On digitalis	80	250	+ 3.8	62.3	4.01	2.10	50	26.2
D. de C.				27/ 8/42	Class II On digitalis	77	237	− 0.6	66.1	3.58	1.87	46	24.3
19	F	33	1.63	14/10/42	Class II On digitalis	68	246	+19.7	68.2	3.61	2.21	53	32.5
L. F.				15/10/42	Class II On digitalis	62	233	+13.7	65.5	3.55	2.18	57	35.0
20	M	17	1.58	3/12/41	Class II On digitalis	64	233	0	74.5	3.13	1.98	49	31.0
J. A.													
21	M	34	1.76	3/12/42	Class II On digitalis	82	211	−12.1	60.0	3.52	2.00	43	24.4
V. C.													
22	M	66	1.72	2/ 5/42	Class II On digitalis	75	258	+18.9	94.7	2.72	1.58	36	20.9
J. R.			1.76	20/10/42	Class III On digitalis	78	250	+12.6	110.6	2.26	1.28	29	16.5

TABLE III

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O_2 DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	$M.^2$			PER MIN.	C.C. PER MIN.	%	C.C. PER LITER	LITERS PER MIN.	$1/M.^2$ PER MIN.	C.C.	C.C./$M.^2$
Mitral Stenosis and Insufficiency, Aortic Insufficiency													
23 D. R.	F	47	1.56	19/ 9/42	Class II (Sinus rhythm) Without treatment	73	207	+ 6.6	65.6	3.16	2.02	43	27.5
Mitral Stenosis and Insufficiency, Tricuspid Stenosis and Insufficiency													
24 J. de C.	F	46	1.66	29/ 8/42	Class II (Auricular fibrillation) On digitalis	82	239	+15.8	74.0	3.23	1.95	39	23.7
25 M. de C.	F	50	1.47	23/ 2/45	Class IV (Auricular fibrillation) Without treatment	98	223	+22.2	97.4	2.29	1.56	23	15.9
Mitral Stenosis and Insufficiency, Interauricular Septal Defect													
26	F	39	1.55	6/ 4/42	Class II (Auricular fibrillation) On digitalis	58	226	+14.9	60.5	3.74	2.41	64	41.3
L. de. E.				8/ 4/42	Class II (Auricular fibrillation) On digitalis	58	229	+17.2	56.0	4.09	2.64	70	45.2
27 A. de C.	F	44	1.52	10/ 9/42	Class II (Sinus rhythm) Without treatment	60	195	+ 3.3	61.2	3.19	2.10	53	35.0
28 A. de U.	F	39	1.62	6/10/42	Class III (Auricular fibrillation) On digitalis	69	223	+ 9.3	83.5	2.67	1.65	38	23.5
				7/10/42	Class III (Auricular fibrillation) On digitalis	70	225	+10.1	92.5	2.43	1.50	34	21.0

TABLE IV

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O_2 DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	$M.^2$			PER MIN.	C.C. PER LITER	%	C.C. PER LITER	LITERS PER MIN.	$1/M.^2$ PER MIN.	C.C.	C.C./$M.^2$
Aortic Insufficiency													
29 R. S.	M	17	1.81	26/11/42	Class I Without treatment	76	284	+ 5.6	53.3	5.33	2.94	70	38.8
30 B. N.	M	53	1.98	12/ 2/43	Class III On digitalis	70	306	+19.2	68.2	4.49	2.27	64	32.3
				13/ 2/43	Class III On digitalis	70	306	+19.2	68.0	4.50	2.27	64	32.3
Aortic Stenosis and Insufficiency													
31 M. P.	M	60	1.69	20/ 4/43	Class II Without treatment	76	224	+ 3.5	62.9	3.56	2.10	47	27.8
				21/ 4/43	Class II Without treatment	76	219	+ 1.3	63.1	3.47	2.05	46	27.2
				20/ 5/43	Class II On digitalis	72	189	−12.4	58.7	3.22	1.91	45	26.5
32 A. C.	M	42	1.54	13/ 8/42	Class III Without treatment	69	245	+19.4	86.7	2.82	1.83	41	26.5
				20/ 8/42	Class III Without treatment	65	227	+10.6	87.0	2.61	1.69	40	26.1

TABLE V. HYPERTENSIVE AND CORONARY HEART DISEASE

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O_2 DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	$M.^2$			PER MIN.	C.C. PER LITER	%	C.C. PER LITER	LITERS PER MIN.	$1/M.^2$ PER MIN.	C.C.	$C.C./M.^2$
33 M. P.	M	56	1.86	17/11/41	Class I (Auricular fibrillation) Without treatment	72	257	+ 8.0	50.5	5.09	2.73	71	38.0
			1.88	10/12/41	Class I (Auricular fibrillation) Without treatment	75	238	− 2.4	48.4	4.92	2.62	66	34.9
34 C. D.	M	70	1.95	2/10/42	Class II (Auricular flutter) Without treatment	54	240	− 1.1	56.6	4.24	2.17	78	40.0
				3/10/42	Class II (Auricular flutter) Without treatment	52	232	− 4.1	63.3	3.66	1.88	70	35.9
35 V. P.	M	59	1.85	22/ 5/43	Class II (Sinus rhythm) Without treatment	64	224	− 6.7	62.5	3.59	1.94	56	30.3
36 F. F.	M	59	1.77	13/ 9/44	Class II (Sinus rhythm) Without treatment	74	258	+12.5	64.6	3.99	2.25	54	30.5
				17/ 9/44	Class II (Sinus rhythm) Without treatment	70	264	+15.2	59.7	4.42	2.49	63	33.6
37 O. de R.	F	52	1.67	6/10/43	Class III (Auricular fibrillation) On digitalis	60	231	+14.3	85.6	2.70	1.62	45	26.9
38 D. P.	M	63	1.72	4/10/44	Class III (Sinus rhythm) Without treatment	80	237	+ 9.3	68.4	3.46	2.01	43	25.2
39 J. de C.	F	63	1.48	9/ 2/43	Class III (Auricular fibrillation) Without treatment	58	160	− 7.9	67.9	2.35	1.59	41	27.7
				10/ 2/43	Class III (Auricular fibrillation) Without treatment	56	167	− 4.1	71.8	2.32	1.57	41	27.7
40 M. de S.	F	68	1.48	5/12/42	Class III (Sinus rhythm) Without treatment	95	222	+27.9	77.8	2.85	1.93	30	20.3
41 C. A.	M	54	1.88	18/11/44	Class IV (Sinus rhythm) Without treatment	85	280	+14.9	92.0	3.04	1.62	36	19.1
			1.87	5/12/44	Class III (Sinus rhythm) On digitalis	67	242	0	64.9	3.73	1.99	56	29.9
42 I. de O.	F	51	1.59	29/ 4/43	Class IV (Auricular fibrillation) On digitalis	58	202	+ 3.7	93.9	2.15	1.35	37	23.3
				4/ 5/43	Class IV (Auricular fibrillation) On digitalis	80	224	+16.3	77.9	2.87	1.81	36	22.6

TABLE VI. AVERAGE RESULTS OBTAINED GROUPING THE CASES ACCORDING TO THEIR FUNCTIONAL CAPACITY

FUNCTIONAL CAPACITY	HEART RATE				ARTERIOVENOUS OXYGEN DIFFERENCE		CARDIAC INDEX		SYSTOLIC OUTPUT PER SQUARE METER OF BODY SURFACE	
	MITRAL GROUP		AORTIC, HYPERTENSIVE, AND CORONARY GROUP							
	NUMBER OF CASES	AVERAGE PER MIN.	NUMBER OF CASES	AVERAGE PER MIN.	NUMBER OF CASES	AVERAGE AND STANDARD DEVIATION C.C. PER LITER	NUMBER OF CASES	AVERAGE AND STANDARD DEVIATION L./M.^{2}	NUMBER OF CASES	AVERAGE AND STANDARD DEVIATION C.C./M.^{2}
Class I	3	63	2	74	5	62.2 ±14.61	5	2.35 ±0.44	6	35.3 ± 6.90
Class II	19	70	4	66	23	66.9 ± 8.88	23	2.03 ±0.24	23	29.8 ± 5.50
Class III	6	83	7	71	12	81.0 ±13.71	12	1.73 ±0.30	13	23.8 ± 4.67
Class IV	1	98	2	77	3	91.8	3	1.58	3	19.3
Normal controls	63				17	60.4 ± 7.36	17	2.27 ±0.24	17	35.4 ± 3.14

normal and of the four cardiac groups is represented by a horizontal line, shows that the individual values are evenly distributed regardless of the diagnosis. In Table VI the results obtained by grouping the cases according to their functional capacity, disregarding their diagnosis, are presented.

DISCUSSION

The determination of cardiac output by a foreign gas method in patients with interauricular septal defect and mitral disease can be criticized, since in this condition the blood which passes from the left to the right auricle produces an abnormally rapid recirculation. We do not know whether or not in other similar cases this rapid recirculation can be an important source of error. In our patients it seems to have been of little importance since we could obtain similar values in two pairs of successive samples of the same rebreathing period.

Patient R. S. (uncomplicated aortic regurgitation, Class I, No. 29) showed a cardiac index well above the normal limit. Although the first possible explanation of this finding is a modification of the basal conditions, this could be ruled out because the patient was quiet and cooperative and the basal metabolic rate was normal. On the other hand, Starr and Gamble[48] stated that similar results have been obtained by Ewig and Hinsberg,[18] Starr and collaborators,[47] Syllaba,[64] and Bock.[65] Even though the methods employed by some of these authors are open to objection, the fact that similar results were obtained by several investigators in patients without failure, where special technical difficulties are not expected, gives support to our findings.

Since the possibility exists that in aortic insufficiency the valvular defect might modify the cardiac index independently of the functional capacity, we eliminated patients with uncomplicated aortic insufficiency in calculating the average cardiac index of each functional group.

The difference between the cardiac index of normal subjects (2.27) and that of cardiac patients of Class I (2.35) is 0.08 ± 0.20, which is not statistically significant. The difference between the average cardiac index of patients of Class I (2.35) and of patients of Class II (2.03) is 0.32 ± 0.20, which likewise is not significant. Comparison of the normal persons (cardiac index, 2.27) with patients of Class II (cardiac index, 2.03) shows that the difference of the averages (0.24 ± 0.078) equals slightly more than three times its standard deviation, which is highly significant. Although the difference between patients in Class I and those in Class II is greater than that between normal persons and patients in Class II, it is not statistically significant in the former case because of the small number of patients in Class I (five patients). Comparison between the averages of individuals in Class II (cardiac index, 2.03) and those in Class III (cardiac index, 1.73) shows that the difference (0.30 ± 0.10) equals three times its standard deviation and is, therefore, statistically significant. Between persons in Class III (cardiac index, 1.73) and persons in Class IV (cardiac index, 1.58) the difference is 0.15. We did not determine a statistical difference with Class IV because of the small number of cases in the latter.

The results obtained in our series of hypertensive, coronary, and valvular diseases, excepting uncomplicated aortic regurgitation, led to the conclusion that the patients belonging to Class I (with no limitation of physical activity) maintain at rest a normal cardiac output. Patients of Class II (slight limitation of physical activity) on the whole have a diminished cardiac output even at rest, but their cardiac index is significantly greater than that of patients in Class III (marked limitation of physical activity). The small number of patients in Class IV (unable to carry on any physical activity without discomfort) prevented our drawing conclusions concerning this group, in spite of the low value of the average cardiac index, i. e., 1.58 liters per square meter per minute (the lowest value of any class). In patients with congestive heart failure, comparable to those included in Class IV, McGuire and his co-workers[58] found an average cardiac index of 1.52 ± 0.06 and Stewart and his associates[61] found an index of 1.42. These results obtained with the acetylene method, taking three samples, give support to our findings and indicate that in patients in Class IV the cardiac output reaches its lowest level.

The normal values which we obtained in patients in Class I are in accord with the observations of McMichael[52] made in the same type of patients and differ from the results of Stewart and his associates,[61] who state that patients with organic heart disease without failure have a decreased cardiac index.

The above results show that most of the patients with heart failure have a diminished cardiac output and suggest that there is an inverse correlation between the degree of cardiac failure and the cardiac output. However, in some subjects, in spite of their cardiac failure, the cardiac output was within normal values, but this occurred less frequently in the more advanced stages of the disease. The possibility exists that, in some cases, even though there is a diminution of the cardiac output, the values reached are within the lower normal limits, for instance, an index of 2.5 to 2.0, the latter still being a normal figure. It is also possible that an increase in the metabolic rate, such as is frequently seen in heart failure, or variations in the other mechanisms which control the cardiac output (venous pressure, pulmonary ventilation, and so forth) may explain the differences found in the patients included in each class. The general trend of the cardiac output towards lower values in heart failure and the importance of the extracardiac factors are at present accepted by all investigators of this subject (Altschule,[66] McGuire and collaborators,[57-59] McMichael,[52] Harrison,[55] Stewart and his associates,[60, 61] and others).

Some observers, however, notably Harrison and his co-workers[54] and Harrison,[55] believe that there is no correlation between the cardiac output and the degree of heart failure, and attribute this lack of correlation to the influence of the various extracardiac factors. On the other hand, several investigators (Stewart and collaborators[60, 61] and McGuire and collaborators[58, 59]) admit that a correlation can be drawn between cardiac output and the functional capacity of the heart, the exceptions being explained on the basis of extracardiac factors. Our findings support these conclusions. It should be emphasized that the correlation noted by Stewart and collaborators[60] between the number or type of valvular lesions and the functional alterations was not seen in our study.

The arteriovenous oxygen difference of patients in Class I (62.2 c.c. per liter) is approximately the same as that of normal subjects (60.4 c.c. per liter). The average values of the arteriovenous oxygen difference of patients of Class I and Class II (66.9 c.c. per liter) do not differ significantly (4.7 ± 6.79). On the other hand, the difference between the average values for patients of Class II and that of the normal persons is 6.5 ± 2.57, which means that the difference is very probably real. The arteriovenous oxygen difference of patients in Class III (81.0) compared with patients in Class II shows a difference of 14.1 ± 3.37, which is statistically significant. Patients in Class IV have an arteriovenous oxygen difference of 91.8, i. e., 10.8 greater than that of patients in Class III. No statistical determinations were carried out in Group IV because of the small number of cases.

These figures show that cardiac patients without failure maintain a practically normal arteriovenous oxygen difference. Where various degrees of failure exist, the arteriovenous oxygen difference increases, suggesting a correlation with the degree of the failure. The arteriovenous oxygen difference is an important index of the circulatory function. However, the wide scattering of the different values within normal as well as within cardiac groups makes necessary a great deal of caution in judging individual results.

The heart rate of patients with mitral stenosis shows a different behavior when compared with the behavior of the rate of patients with other types of heart disease. In calculating the averages in the group of patients with a mitral lesion, we excluded Case C. T. (mitral insufficiency and stenosis, sinus rhythm, No. 1, Class I) because of the slightly elevated metabolic rate which, in the absence of heart failure, indicated the possibility of a mild degree of hyperthyroidism. We considered +15 per cent to be the upper normal metabolic rate. For similar reasons we used only the fourth and fifth determinations made in Patient R. C. (mitral stenosis and insufficiency, auricular fibrillation, No. 15, Class II), whose basal metabolic rate was normal.

The results obtained show that in the cases with failure there was a general trend toward an increased heart rate, although there were differences within the various diagnostic groups. Patients with mitral valve lesions with no failure (Class I) showed a normal heart rate; those with various degrees of failure (Classes II, III, and IV) presented an increased cardiac rate which was proportional to the degree of the failure. On the other hand, in the other types of heart disease we could not observe any relation between functional capacity and heart rate.

The systolic output per square meter of body surface, up to now used almost exclusively by Scandinavian investigators, proved to be a useful index of circulatory modifications in heart failure. As the results did not show important differences in the various types of heart disease, it seemed reasonable to consider together all the cases of valvular, hypertensive, and coronary heart disease. The patients belonging to Class I had an average stroke volume per square meter of 35.3 c.c., nearly equal to that of normal subjects (35.4). Patients in Class II had a lower average (29.8), but the difference between patients in Class II and

those in Class I (5.5 ± 3.04) was not statistically significant. This may have been due to the small number of cases in Class I. The difference in stroke volume in normal persons and in patients in Class II was 5.6 ± 1.44 (statistically significant); the same holds for the difference between patients in Classes II and III (6.0 ± 1.73). Subjects in Class IV showed the lowest index (19.3), with a difference with respect to patients in Class III of 4.5. The figures suggest that an inverse correlation does exist between systolic output and the degree of heart failure.

SUMMARY AND CONCLUSIONS

The cardiac output under basal conditions was studied in forty-two patients with different types of valvular, hypertensive, or coronary heart disease, and in seventeen normal subjects. Grollman's acetylene method with four samples was used. The cardiac patients were grouped in four classes according to their functional capacity, following the criteria and nomenclature of the New York Heart Association. The following results, expressed as an average for each group, were obtained:

1. The cardiac index was 2.27 liters per square meter per minute ± 0.06 in the normal control group, 2.35 ± 0.19 in patients in Class I, 2.03 ± 0.05 in patients in Class II, 1.73 ± 0.087 in patients in Class III, and 1.58 in those in Class IV.

The differences found were statistically significant between the normal group and those in Class II, and between persons in Classes II and III, suggesting an inverse correlation between the degree of cardiac failure and the cardiac output.

2. The arteriovenous oxygen difference was 60.4 c.c. per liter of blood ± 1.78 in the normal group, 62.2 ± 6.53 in patients in Class I, 66.9 ± 1.85 in those in Class II, 81.0 ± 3.96 in persons in Class III, and 91.8 in patients in Class IV.

The difference between normal subjects and subjects in Class II was probably real, and the difference was statistically significant between subjects in Class II and subjects in Class III. This suggested a direct correlation between the degree of cardiac failure and the increase in arteriovenous oxygen difference.

3. The behavior of the heart rate was different in patients with mitral valve disease and in those with aortic, hypertensive, and coronary artery disease. The heart rate in the normal group averaged 63 per minute.

In the mitral patients the heart rate was 63 per minute in those in Class I, 70 in those in Class II, 83 in those in Class III, and 98 in Class IV. The heart rate in patients with other types of disease was 74 in those in Class I, 66 in those in Class II, 71 in those in Class III, and in 77 in patients in Class IV.

Although statistical determinations of these data were not carried out, the corresponding results in each group seemed to indicate that, in the mitral patients without failure (Class I), the heart rate was within the normal range, increasing in the presence of failure and according to the severity of the latter. In the aortic, hypertensive, or coronary groups, the behavior of the cardiac rate was rather irregular.

4. The systolic output per square meter of body surface was 35.4 c.c. ± 0.76 in the normal group, 35.3 ± 2.81 in patients in Class I, 29.8 ± 1.14 in those in Class II, 23.8 ± 1.29 in those in Class III, and 19.3 in patients in Class IV.

The differences were statistically significant between the normal group and those in Class II and between patients in Classes II and III, suggesting that an inverse correlation exists between heart failure and systolic output.

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RENIN IN ESSENTIAL HYPERTENSION

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THERE has been much discussion recently on the part which the kidney plays in the production of human hypertension. Recent work seems to indicate that renin is the pressor substance involved in the mechanism of renal hypertension. Renin has been found in the arterial and renal venous blood of dogs having hypertension of recent onset with severe reduction of the renal blood flow but not in the renal or arterial blood of chronically hypertensive dogs.[1] Using the method of Leloir and his co-workers[2] we were able, in 1943,[3] to detect renin in two patients who had severe acute glomerulonephritis. These findings agree with those of Dexter and Haynes[4] who, with a similar method, detected renin in one patient with eclampsia, two with severe pre-eclampsia, and one with fulminating glomerulonephritis, but not in patients with other types of hypertension.

It seemed appropriate to repeat these investigations, using for the detection of renin the indirect method of Muñoz and his associates.[5] This method is capable of detecting about 0.1 unit of human renin in 10 c.c. of plasma. Its sensitivity is about five to ten times greater than the direct method of Leloir and his co-workers.[2]

MATERIAL AND METHODS

This investigation was carried out on twenty-three hypertensive patients. In all of them the diagnosis was essential hypertension. The existence of medical or surgical renal disease or of other known causes of hypertension were excluded as far as possible. The patients were observed over long periods of time, and several determinations of the blood pressure were made. The figure that appears in the table represents the average. All of the patients belonged to Groups II, III, and IV of the Keith, Wagener, and Barker classification.[6] Seven patients were in Group II, eight were in Group III, and eight were in Group IV. Five patients in the last group were in an advanced stage of malignant hypertension and died soon after the estimation of renin was made.

Blood was taken in most cases by venous puncture and in some by arterial puncture. Sodium citrate or heparin was used to prevent coagulation. The blood was immediately centrifuged. The plasma was transferred to a tube and the determinations were carried out within a few hours. Sometimes the estimations were deferred for a day or two; the plasma was kept in the icebox in the meantime.

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For the detection of renin, the method of Muñoz and collaborators[5] was used. The amount of renin is estimated by measuring the amount of hypertensinogen which it destroys during a four-hour incubation period. A measured amount of bovine hypertensinogen (about 1 unit) is incubated with 10 c.c. of the human plasma in which the determination is to be carried out; red cell hypertensinase and 0.6 c.c. of a 1 per cent solution of merthiolate (Lilly) as a preservative are added. A control tube is prepared in which human plasma and bovine hypertensinogen are incubated separately (Fig. 1).

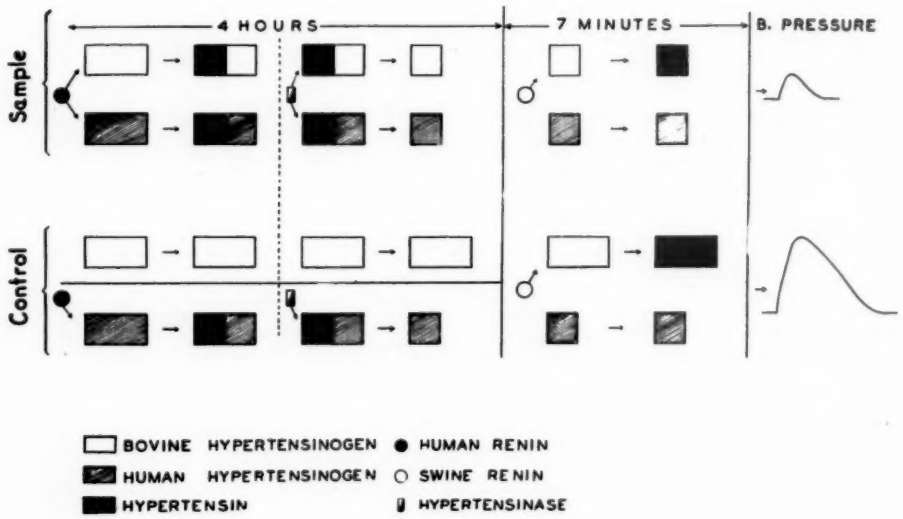

Fig. 1.—Diagram showing the reactions involved in the assay of human renin. The tube in which the determination is to be carried out is incubated four hours at 37°C. During this period, human renin, if present, transforms part of the hypertensinogen (bovine and human) into hypertensin, which will be destroyed by the hypertensinase present. These reactions have been represented in two steps, separated by the dotted line. Actually, they occur simultaneously. After the four-hour period, the bovine hypertensinogen left is estimated by incubating the plasma for seven minutes with swine renin which does not act upon human hypertensinogen. The hypertensin formed is estimated by its pressor effect when injected into an anesthetized dog intravenously. In the control tube, human plasma and bovine hypertensinogen are incubated separately. This is represented in the diagram by the horizontal line dividing the control.

During the four-hour incubation period, renin, if present, transforms part of the bovine and human hypertensinogen, and the hypertensin that is formed is destroyed by the hypertensinase. The bovine hypertensinogen remaining is then estimated; advantage is taken of the specificity of pig renin. An excess of pig renin transforms all of the bovine but none of the human hypertensinogen into hypertensin in seven minutes. Because of the short incubation time, the hypertensin formed is not destroyed by the hypertensinase. After precipitation with alcohol, the hypertensin content of each tube is estimated by the extent to which it raises blood pressure in the anesthetized dog. Fig. 1 presents a graphic description of the reactions involved.

By the use of the present method, amounts of renin as small as 0.1 unit* in 10 c.c. of plasma can be detected semiquantitatively. Three tubes were prepared. The first, hereafter referred to as the sample tube, contained the patient's plasma, bovine hypertensinogen, and hypertensinase, as described before. Tube 2 contained 10 c.c. of plasma, and Tube 3 contained the bovine hypertensinogen. The three tubes were incubated at 37°C. for a period of four to eleven hours, after which the contents of Tubes 2 and 3 were mixed to make the control tube. Three cubic centimeters of pig renin were added to the sample tube and to the control tube, and both were incubated for seven minutes. In other cases a fourth tube was added, containing human plasma (10 c.c.), bovine hypertensinogen, hypertensinase, and a measured amount of human renin (about 0.1 to 0.2 unit). We shall refer to this fourth tube as the standard tube. Determinations on the contents of this tube were carried out as in Tube 1.

After the short incubation period, the contents of the tubes were precipitated with 3 volumes of 95 per cent alcohol, the alcohol was distilled off *in vacuo*, and the aqueous residue was injected intravenously into an anesthetized dog. The blood pressure rises, in millimeters of mercury, were recorded on a smoked drum.

RESULTS

Table I summarizes the results. In every case the results are given according to the order in which the samples were injected into the dog. Since the sensitivity of the animal changes with time, as shown by the pressor response to a unit of hypertensin, it is important to know when the injection is made in order to compare the rise of pressure resulting from the injection of the solution in both the sample and control tubes.

The ratio $\frac{\text{mm. Hg rise of sample tube}}{\text{mm. Hg rise of control tube}} \times 100$ was calculated as follows: If the sample and the control tubes were tested, one immediately after the other, the rises in blood pressure were compared directly, even if the sensitivity of the dog changed, as indicated by a change in pressor response to 1 unit of hypertensin injected before and after the samples. If a standard tube containing renin was injected between the sample and the control tubes, the pressor response of both sample and control tubes was compared with the nearest hypertensin unit and the calculated ratio $\frac{\text{sample tube}}{\text{unit of hypertensin}}$ was compared as before. In the ratio $\frac{\text{standard with renin}}{\text{control tube}} \times 100$, the rises in blood pressure were directly compared.

For example, in Case A. de R., the rises in blood pressure in millimeters of mercury were as follows: unit of hypertensin = 30; sample tube = 15; standard with renin = 8; control = 16; hypertensin unit = 32. We first calculated the

*A unit of renin is the amount which, when incubated two hours with an excess of hypertensinogen, yields 0.5 unit of hypertensin.

TABLE I. RESULTS OF THE ASSAY OF HUMAN RENIN IN TWENTY-THREE PATIENTS WITH ESSENTIAL HYPERTENSION*

PATIENT	SEVERITY OF HYPERTENSION (KEITH ET AL., 1939)	BLOOD PRESSURE OF PATIENT (SYSTOLIC AND DIASTOLIC)	BLOOD PRESSURE RISE PRODUCED BY								$\frac{\text{SAMPLE}}{\text{CONTROL}} \times 100$	$\frac{\text{STANDARD}}{\text{CONTROL}} \times 100$	TIME OF INCUBATION
			ONE UNIT OF HYPERTENSIN	SAMPLE TUBE	STANDARD TUBE	ONE UNIT OF HYPERTENSIN	CONTROL TUBE	ONE UNIT OF HYPERTENSIN	STANDARD TUBE	ONE UNIT OF HYPERTENSIN			
	GROUP	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG			HOURS
I. de G.	II	185/120	29	22		22	14				117		4
S. M.	II	200/120	22	25			18	20			139		4
R. N.	II	198/135	36	30			20				150		4
J. F.	II	190/126	56	50			47	40			106		4
J. L. de C.	II	220/130	40	30			25	30			112		4
A. de R.	II	220/140	30	15	8‖		16	32			100	50	4
M. C.	II	260/145	43	33			29		20‡	30	113	69	11
H. D. de F.	III	240/120	20	22			15				146		4
			30	23	8‖		23	30			100	35	4
J. M. de M.	III	260/150	45	36			35	48			103		4
M. C. de F.	III	245/140	56	33	27§		23	34			114	100	4
A. F	III	210/110	34	21	14§		30				70	47	4
L. A.	III	230/130	30	18	9‖		18	30			100	50	4
M. S.	III	240/120	30	30			27		15‡	50	111	55	11
M. G. de C.	III	250/100	50	30			26		10‡	34	115	39	11
A. L.	III	205/110	60	50			35				143		10
M. P. de C.	IV	235/140	33	17			17	33			100		4
J. T.	IV	280/160	40	15			14	40			107		4
M. de S.	IV	250/130	32	22	18‖		22				100	82	4
A. P.†	IV	245/135	60	40			32	70			125		10
C. M.†	IV	240/120	70	30			30				100		10
I. de M.†	IV	270/160	48	32			40	48			80		4
			48	40	20§		30	40			111	67	4
F. E. G.†	IV	250/155	38	26			24	38			108		4
			28	18	9‡		20	32			103	45	4
D. M.†	IV	250/140	40	20			20			50	100		8

*The pressor responses are tabulated according to the order in which the samples were injected into the anesthetized dog.
†Malignant hypertension.
‡With 0.002 c.c. of a human renin solution containing 50 to 60 units per cubic centimeter.
§With 0.005 c.c. of a human renin solution containing 20 to 30 units per cubic centimeter.
‖With 0.01 c.c. of a human renin solution containing 20 to 30 units per cubic centimeter.

ratio $\frac{\text{sample tube}}{\text{unit of hypertensin}} = \frac{15}{30} = 0.5$ and $\frac{\text{control tube}}{\text{unit of hypertensin}} = \frac{16}{32} = 0.5$, using the nearest value obtained for the unit of standard hypertensin. Then the ratio $\frac{\text{sample tube}}{\text{control tube}} \times 100 = \frac{0.5}{0.5} \times 100 = 100$ was calculated. For the ratio $\frac{\text{standard with renin}}{\text{control tube}} \times 100 = \frac{8}{16} \times 100 = 50$, the rises were directly compared.

Table I shows that in 18 of the 26 cases, the ratio $\frac{\text{sample tube}}{\text{control tube}} \times 100$ ranged between 100 and 115, indicating that both tubes contained approximately the same quantities of hypertensinogen, which in turn indicates that renin was not present in the sample plasma. In two cases the diminution of the hyper-

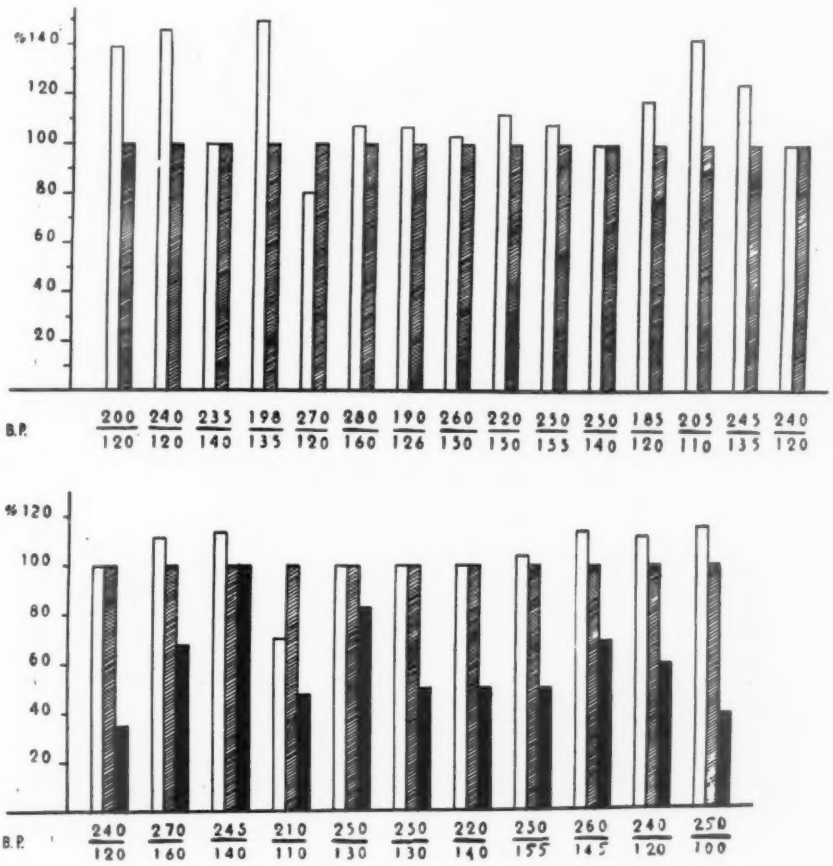

Fig. 2.—Ordinates represent the values of the $\frac{\text{sample}}{\text{control}} \times 100$ ratios. White columns are the ratios corresponding to the sample tubes; black columns represent the ratios of the tubes to which a small amount (0.1 to 0.2 unit) of human renin was added (standard tube). The shaded columns represent a ratio of 100. Values under 100 indicate the presence of renin. For interpretation of the data on the two patients in whom values were low, as indicated by short white columns, see text. The figures on the bottom of the columns are the values of the blood pressure of each patient.

With 0.01 c.c. of a human renin solution containing 20 to 30 units per cubic centimeter.

tensinogen in the sample tube suggested the presence of renin. In one of them, however, a duplicate determination gave no indication of the presence of renin.

In six cases the ratio ranged between 117 and 150. This may have been due to changes in the sensitivity of the dog to hypertensin, especially in the extreme cases with a ratio of 146, 150, and 143. In these cases, no tests with the standard hypertensin unit were made after the injection of the control tube. On the whole, the results seem to indicate a small increase of pressor action in the sample tube. At present we are unable to explain these results.

All except one of the standard tubes with added human renin showed a ratio ranging from 82 to 35. This indicated that the minute amount of renin added (0.1 to 0.2 unit) was, with only one exception, easily detected.

DISCUSSION

Using the methods available, renin has not been detected in the plasma of patients in either the benign or the malignant phase of essential hypertension. These findings, however, do not disprove the renal origin of human hypertension. Actually, renin has been detected in the plasma of dogs after a short period of complete ischemia of the kidney,[7] and in the renal and arterial blood in the acute phase of hypertension produced by partial but severe ischemia of the kidney.[1] On the other hand, renin has not been demonstrated in the renal or arterial blood of chronically hypertensive dogs.[1, 8] In the human being, small amounts of renin were found in the renal vein after a short period of complete ischemia[9] and in the acute hypertension of a few cases of eclampsia and fulminating glomerulonephritis[4] but not in chronic hypertension. Since the results obtained in human hypertension agree with those obtained in experimental renal hypertension of the dog, we can conclude that the absence of renin cannot rule out the renal origin of essential hypertension.

The fact that it has not been possible to detect renin in the blood of chronically hypertensive dogs or of patients with essential hypertension neither supports nor negates the hypothesis that renin is the pressor substance involved. Whether renin is present in such minute amounts that it cannot be detected by the method used, or whether it does not exist at all in these patients, cannot be decided at present.

Since renin is found by existing methods in the acute phase of renal hypertensive disease and in complete ischemia of the kidney but not in the chronic stage of the disease, the possibility exists that renin may appear in the blood as an autolytic product of the kidney. It is also possible that renin may initiate the pressor mechanism which later proceeds without its presence.

CONCLUSIONS

Renin has not been detected in the arterial or venous plasma of twenty-three patients suffering from essential hypertension with and without impairment of renal function.

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PARASTERNAL LEADS IN TRICUSPID INSUFFICIENCY

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THE purpose of this communication is to illustrate the electrocardiograms of two cases presenting clinical signs of tricuspid insufficiency and right auricular enlargement. In these cases, striking and unusual auricular deflections of the diphasic (+ —) type are found in leads from the right side of the precordium. Their mode of production and possible significance have been a source of interest and speculation to us and will be discussed.

Unusual P waves in the precordial electrocardiogram have been the subject of only a few previous papers. Burton and Mehlman[1] published a report of a case of spontaneous pneumothorax of the right side of the chest in which a deeply inverted P wave (13 mm.) occurred in Lead CF_2. Upon partial release of the pneumothorax and during spontaneous resolution, this precordial P wave became diphasic and had a configuration similar to those described in the present report. Gertz,[2] also, reported a diphasic P wave in a lead taken at the C_2 position in a case in which a calcareous tuberculous lesion of the upper left lung caused traction on the heart. These cases differ, it will be noted, from the two we describe in that an extracardiac factor produced displacement of the heart toward the left and thus placed the right auricle beneath the area of the precordial electrode. Auricular deflections of this sort have apparently not been observed in the frequent clinical combination of cardiac decompensation with right pleural effusion and displacement of the heart toward the left.

Pardee[3] has reported two cases of uncomplicated tricuspid stenosis with high, peaked P waves in the limb leads and discussed the findings of Winternitz who relates the size and shape of these waves to auricular hypertrophy. Pardee concludes that the height of the wave in limb leads is due to right auricular hypertrophy, and that the notching and increased duration is due to involvement of both auricles.

Szekely[4] recently found no correlation between the size of the right auricle and the amplitude of the P waves as recorded in chest leads taken at the third intercostal space to the right of the sternum. He suggested as possible factors the anatomic position of the right auricle and its juxtaposition to the anterior chest wall.

A case of mitral stenosis and one of congenital heart disease, in which the electrocardiograms show an auricular complex in CF_1 similar to those in our cases, are illustrated by Sigler.[5] The P waves were large and of the diphasic (+ —) type. Both of his cases showed right ventricular dilatation and hypertrophy.

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CASE REPORTS

CASE 1.—D. F., a white child, aged 12 years, was admitted to the pediatric floor of Toledo Hospital on Nov. 3, 1945. About three weeks previously, she had had an attack of "flu" from which she had made a satisfactory recovery. About four days prior to admission she rapidly became edematous, dyspneic, and cyanotic.

The past history was essentially negative with the exception of pneumonia in infancy. There had been no primary or secondary manifestations of rheumatic fever. She had been a perfectly normal child with no evidence of congenital heart disease.

Physical examination at the time of admission revealed a well-developed and well-nourished child, acutely and severely ill. The temperature was normal, the heart rate was 90, and the respirations were 22 per minute. Breathing was very difficult in the semiupright position and was accompanied by an expiratory grunt. The lips and nail beds were moderately cyanotic. The face appeared swollen, although the eyelids were not specifically edematous. The tonsils were hypertrophic, but the mucous membranes of the nose and throat were clear. The tongue was dry and furrowed. The neck was puffy and flaccid. No enlargement of the thyroid gland and no adenopathy were present. The jugular veins were not conspicuous. Examination of the lungs by percussion and ausculation revealed no changes, although the diaphragm was somewhat elevated on both sides.

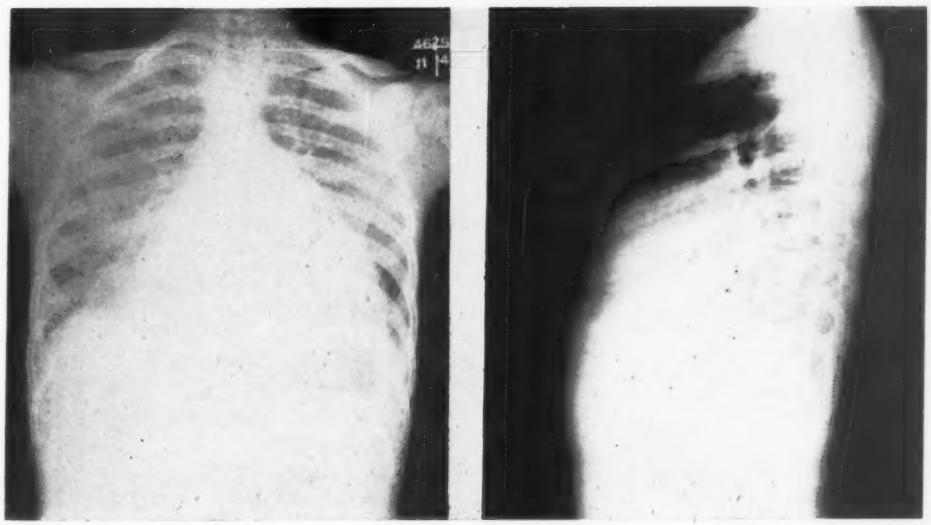


Fig. 1.—Case 1. A-P and lateral roentgenograms.

Examination of the heart showed the rate to be rapid and the rhythm regular. The apical impulse was displaced upward and to the left. A presystolic gallop and a blowing systolic murmur, most marked at the apex, were noted. The sounds were very forceful. An abdominal fluid wave and shifting dullness gave evidence of ascites. There was edema of the right labium, sacrum, and lower extremities. The blood pressure was 110/65.

Other laboratory studies showed 3-plus albuminuria, many hyaline casts, a normal red count and hemoglobin, a leucocytosis of 32,000 with a differential of 52 segmented polys, 25 band forms, 20 mature lymphocytes, 2 monocytes, and 1 eosinophile. The nonprotein nitrogen was 57.3 mg. per cent, and a total protein determination was 5.8 Gm. per cent with 2.5 Gm. of albumin and 3.3 Gm. of globulin (albumin-globulin ratio: 0.76).

Paracentesis was performed, and 1,100 c.c. of cloudy, amber fluid with a specific gravity of 1.013 was withdrawn. This failed to relieve the dyspnea. Two days later her cardiac finding

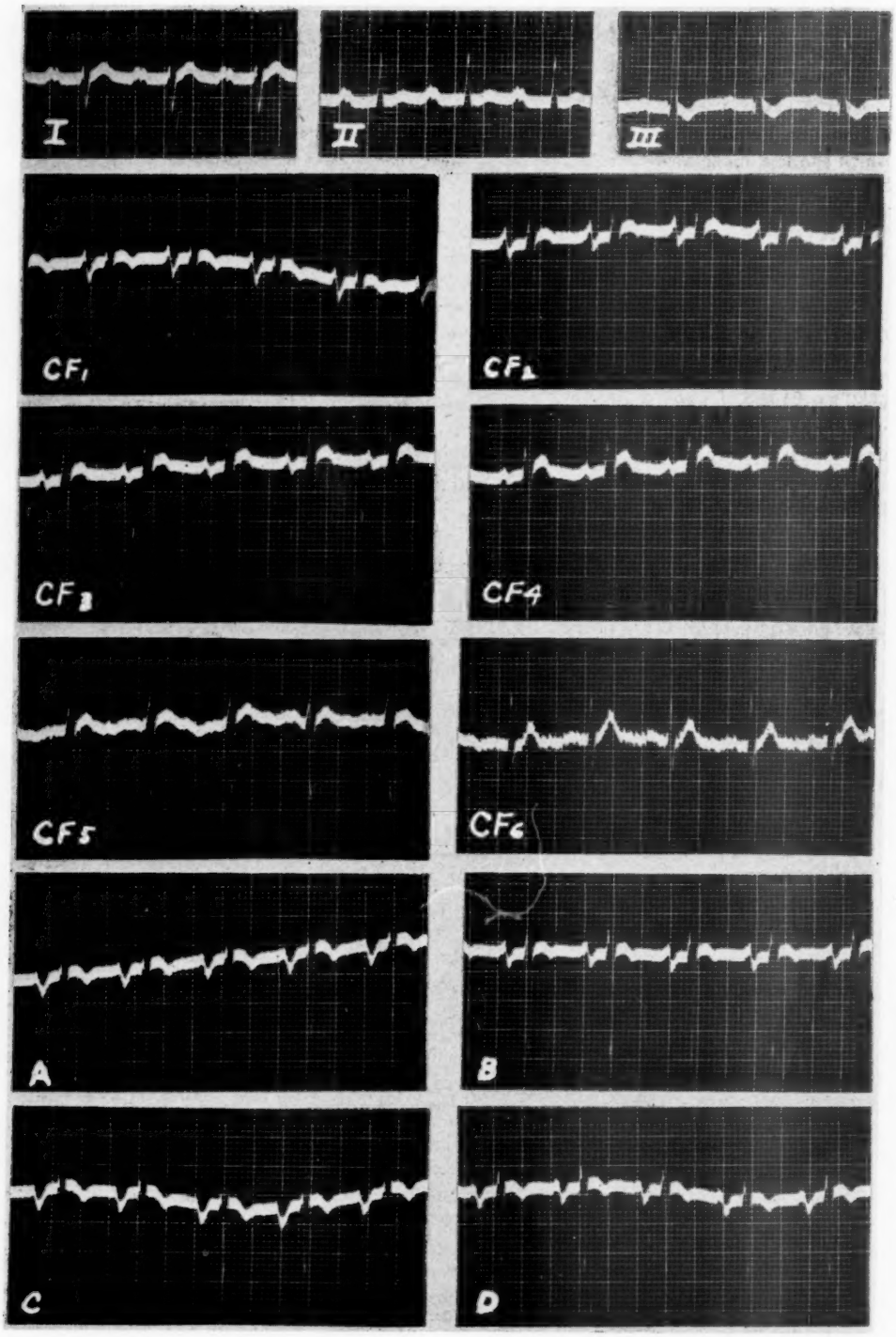


Fig. 2.—Case 1. Conventional leads, taken Nov. 11, 1945, show delayed auriculoventricular conduction time (0.24 second). Precordial leads were taken November 13. Note diphasic P waves in CF_1 and CF_2. *A*, Third intercostal space to the right of the sternum. *B*, Third intercostal space to the left of the sternum. *C*, Second intercostal space to the right of the sternum. *D*, Second intercostal space to the left of the sternum. In these special precordial leads the left leg was used as the site of the indifferent electrode.

had become more definite, and fluoroscopic examination showed uniform pulsations of all borders of the heart. X-ray films of the chest (Fig. 1) were taken, and she was digitalized with marked improvement.

Subsequent laboratory determinations revealed no albuminuria, sedimentation rates of 8 and 15 mm., improvement in plasma proteins, normal urea nitrogen, and normal blood counts. A right pleural effusion developed but rapidly subsided, and this was not present when the electrocardiograms (Fig. 2) were taken.

On November 21, the following observations were recorded: By palpation the apical impulse is at the anterior axillary line. A short systolic thrill is felt in the left fourth intercostal space just within the mammary line. No thrills could be felt over the pulmonic valve area or in the neck over the carotids. There is a loud systolic murmur over the precordium. This murmer is loudest in the mitral area but is transmitted into the infra-axillary space, and posteriorly to the subscapular area. Systolic and diastolic murmurs are heard in the aortic area and down the left border of the sternum. Systolic and diastolic murmurs are heard in the tricuspid area also. The latter murmers blended with the dominant murmurs, but because of the enlargement of the liver and its expansile systolic pulsation, were believed to be of tricuspid origin.

The diagnostic impressions were: (1) aortic regurgitation with possibly some stenosis, (2) mitral regurgitation with possibly some stenosis, and (3) tricuspid regurgitation. The lesions were evidently the result of a recent carditis involving chiefly the aortic and mitral valves complicated by a relative tricuspid insufficiency.

CASE 2.—S. W. J. was an 18-month-old boy. The history as related by the parents told of a normal delivery with no physical defects discovered by the attending physician. No respiratory disturbance nor cyanosis was noticed by the family. At the age of 9 months the child contracted a severe throat infection which necessitated three weeks' hospitalization. After discharge, he suffered a relapse with pulmonary complications. At this time his physician noticed a loud heart murmur which is said to have gradually increased in intensity during and after this illness. Six months ago another physician made the diagnosis of congenital heart disease, which was substantiated with frontal and lateral x-ray films.

On Nov. 11, 1945, the child was examined at the Toledo Clinic. At that time he appeared healthy and well nourished but somewhat backward in both physical and mental development. The chest was of normal shape and symmetrical. There was a large, diffuse impulse visible over the precordium, with the point of maximal intensity in the anterior axillary line. By percussion the right border was 3 to 4 cm. to the right of the sternal margin; the right costophrenic angle was not obliterated. There were no thrills over the precordium or carotids. The liver was of normal size, and the spleen could not be palpated. A long, loud, and rather harsh systolic murmur could be heard over the precordium and was well transmitted into the axilla and also heard posteriorly in the interscapular space. There was also a systolic and early, high-pitched, diastolic murmur of an entirely different tonal quality which was localized to a relatively small area over the lower sternum and the left fourth and fifth intercostal spaces. There was no presystolic element connected with any of these murmurs. During inspiration there was a reduplication of the second sound which was heard best in the second left intercostal space. The pulse rate at the time of the examination was 130 per minute. Arterial pulsation could easily be felt in the popliteal space. The hemoglobin was 96 per cent (Sahli), the red cell count was 5,310,000, and the leucocytes numbered 16,150. A single blood culture was negative. Frontal and lateral x-ray films showed a large globular heart (Fig. 3). The most conspicuous feature was the enlargement of the right auricle and right ventricle. The roentgenogram supported the clinical diagnosis of a congenital heart, the chief lesion being an interventricular septal defect. The electrocardiogram is illustrated in Fig. 3.

It seemed probable that the localized, high-pitched murmur was due to a relative tricuspid insufficiency. Although no enlargement of the liver could be demonstrated, x-ray films showed enlargement of both the right auricle and right ventricle so clearly that relative insufficiency of the tricuspid valve was considered a proper assumption.

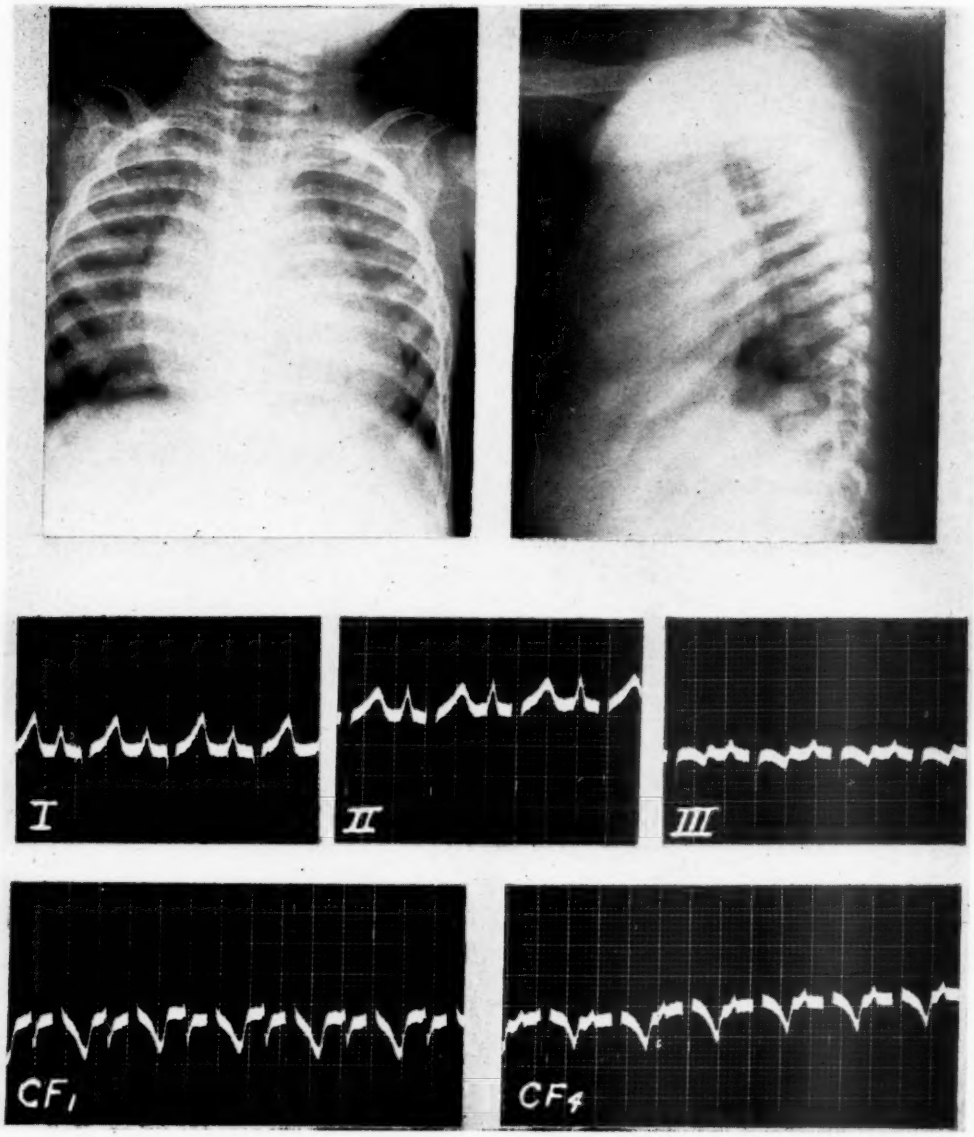


Fig. 3.—Case 2. A-P and lateral (52 inch) roentgenograms. Conventional leads; tall, peaked P waves in I and II, QRS complexes of large amplitude. Note diphasic P wave in CF_1.

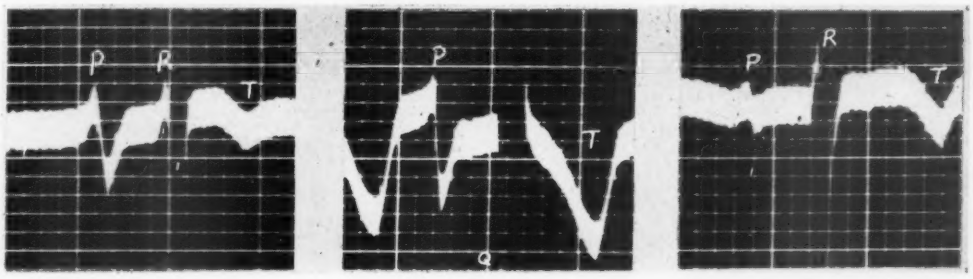
DISCUSSION

Attention is directed to the auricular deflections in Lead CF_1 of both cases. They consist of large, diphasic (+ —) waves with a sharp transition between the positive and negative components (Fig. 4).

These large, diphasic P waves are strikingly similar to auricular complexes seen in esophageal leads. They are also similar in contour to the P waves ob-

tained by Lewis[6] and Wilson, Macleod, and Barker[7] when an electrode was placed on the exposed auricle of a dog. As the peak of maximum positivity of the auricular complex represents the arrival of the excitation wave directly beneath the exploring electrode, we attempted in Case 1 to obtain varying proportions of positivity and negativity by taking parasternal leads from the third and second intercostal spaces; that is, from points nearer to the sinoauricular node. These are illustrated in Fig. 2.

From the character of the auricular complex in Case 2, it would seem that the electrode must have been so placed on the chest as to be in close proximity to the upper portion of the right auricle and not far from the sinoauricular node. This would account for the small initial positivity, the early downward stroke, and the prominent negative component.



A. *B.* *C.*

Fig. 4—Photographic enlargements illustrating the size and shape of the auricular complexes in Lead CF_1. *A*, Case 1; *B*, Case 2; *C*, Lead CF_1 in normal 11-year-old child for comparison.

SUMMARY

Two cases are presented with clinical and x-ray findings of hypertrophy and dilatation of the right ventricle and right auricle, associated with tricuspid insufficiency. The electrocardiograms show large, diphasic P waves in Lead CF_1 such as are normally obtained from esophageal leads and experimentally in direct leads from exposed auricles. It is probable that the proximity of the enlarged right auricle to the anterior chest wall is largely responsible for an auricular wave of this type. Further observations may show that, in tricuspid insufficiency and right auricular enlargement, this characteristic auricular complex in parasternal leads is a significant diagnostic sign.

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PERSISTENCE OF THE JUVENILE PATTERN IN THE PRECORDIAL LEADS OF HEALTHY ADULT NEGROES, WITH REPORT OF ELECTROCARDIOGRAPHIC SURVEY ON THREE HUNDRED NEGRO AND TWO HUNDRED WHITE SUBJECTS

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THE genesis of the T wave in the normal electrocardiogram is still somewhat of a moot point. Irrespective, however, of whether the T wave is the result of organized electrical regression in the ventricles or of the geometric inequality of the complexes derived from the left and the right ventricles, most observers are in agreement that it is upright in electrocardiograms derived from the left side of the chest in adults.[1] The literature contains numerous excellent surveys on large groups of normal individuals which confirm this observation; a few of these will be reviewed briefly.

In 1936, Shipley and Halloran[2] examined the electrocardiograms of 200 normal men and women between the ages of 20 and 35 years and noted that T_4 was inverted in all instances.* Skulasen and Larsen[3] made a similar study of patients between 30 and 50 years of age and found that the T waves from the chest leads were consistently upright. Wood, Wolferth, and Miller[4] studied 299 college students and found three diphasic and one inverted T_4. The latter was in a young man with aortic insufficiency; all the other subjects were normal. In a similar manner, Graybiel and his co-workers[5] made five-lead electrocardiograms (Leads I, II, III, IV F, and IV R) on 1,000 healthy aviators and noted two diphasic T waves in Lead CF_4 and none in Lead CR_4. There were no negative T waves.

When the use of chest leads became common, it was soon apparent that in children the T waves derived from the left side of the chest were very frequently opposite in direction to those obtained from similar positions in adults. The cause of this phenomenon has been studied extensively by various investigators. Since much of this work was done by the old technique in which the adult T_4 is normally inverted, it will be less confusing if we employ wherever possible, and at least during this phase of the discussion, the terms juvenile and adult rather than inverted and upright waves.

Rosenblum and Sampson[6] studied 66 adults and 50 children and noted abnormal T waves in three of the adults. One was in a 16-year-old girl; the other two diverged only slightly from normal. Two of the 50 children demonstrated adult patterns and these were in subjects aged 14½ and 15 years. Dwan and

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*When this study was made, the technique used was such that an inverted T_4 was normal.

Shapiro[7] studied several hundred children with normal and diseased hearts. They reported a high incidence of the juvenile form and, among other conclusions, stated that the findings in routine four-lead electrocardiograms appeared to be constant from day to day. Deeds and Barnes,[8] who examined 50 normal men and a similar group of women, found one subject in whom the T wave in Lead CR_2 approached negativity, while in the other precordial positions the T wave was positive. They concluded that the juvenile form in subjects older than 15 years was to be considered abnormal. Master, Dack, and Jaffe[9] noted juvenile electrocardiograms in 60 per cent of a group of children between the ages of 2 and 15 years. Only 5 per cent of juvenile patterns appeared in the group between 11 and 15 years of age. They suggested that the difference between the adult and juvenile forms was the result of earlier predominance of the right ventricle and of the normally greater relative anteroposterior diameter of the chest in children.

Robinow, Katz, and Bohning[10] noted that juvenile patterns were more frequently found in children who had a thin chest wall and narrow thorax and less commonly in those with a more nearly adult type of chest. They made an exhaustive study of the problem and suggested reasons for the differences noted between adult and juvenile tracings. The known physical differences considered in their paper included the relative right ventricular predominance and axis rotation, the tendency for the heart to lie more horizontally, the greater proportion of the right ventricle lying in the area of left precordial dullness, and the more intimate contact of the heart with the chest wall. All of these are present in childhood. Since the configuration of the tracing is thought to be dependent, to a large extent, upon the conductivity of the tissues interposed between the heart and the chest wall, and since the chest electrode is placed in relation to the bony framework, it does not, therefore, bear the same relation to the heart in children as it does in adults.

The authors suggested that "The variations of T_4 in normal different children could be explained on the variable degrees of transition from the 'puerile' to 'adult' chest type." The same observers also studied electrocardiograms obtained from 20 normal children after a lapse of six to eight months and noted changes toward the adult form in seven instances and away from it in three.

Thus far, reasonable evidence has been obtained from the literature that in adults the T waves in leads derived from the left side of the precordium are normally upright, while in children they are frequently inverted. The theories advanced in explanation of this phenomenon are concerned largely with the differences between adult and juvenile hearts and chests, and the resultant change in relationship of the heart to the chest wall and exploring electrode. However, a number of instances of T_4 abnormality in adults with and without evidence of heart disease have also been noted.

Edeiken, Wolferth, and Wood[11] noted 26 instances of abnormal T_4 in adults in whom the other leads were normal. All of their patients, however, had some type of organic disease. They felt that an abnormal T_4 should not be disregarded and should be an indication for additional study for evidence of heart disease.

They concluded that they had not yet seen an abnormal T_4 in an adult in whom they were confident that "there was no significant heart disease."

Sodeman[12] reported an instance of a reversal of T_4 in a 26-year-old nurse without other evidence of disease. Shanno[13] recorded his observations on electrocardiograms of 100 student nurses, aged 18 to 22 years. There were six instances of T-wave negativity in Lead CF_2, one in Lead CF_3 and none in Lead CF_4. No explanation was offered by either Shanno or Sodeman for these anomalies. Pardee,[14] who observed occasional abnormalities in one chest lead, recommended the use of multiple leads and further observation in such cases.

Dupuy[15] reported five cases of T-wave abnormalities in apparently normal soldiers. Several had T_4 changes, but these were invariably associated with abnormalities in T_1 and T_2 and occurred in individuals who had some type of cardiovascular complaint. Some of the tracings were grossly abnormal but were considered to be functional variants because they were reversible following rest and sedation. He suggested that these variants might be due to cardiac rotation or to anxiety associated with a rapid cardiac rate.

Thompson[16] described interesting electrocardiographic changes which occurred during hyperventilation in susceptible individuals. Here, too, alterations were observed in the T waves of any or all leads in subjects with anxiety neuroses, precordial pain, tachycardia, and hyperventilation. This was considered to be the result of associated alkalosis. It is not improbable, however, that the anomalies recorded by both Dupuy[15] and Thompson[16] during anxiety, tachycardia, and hyperventilation were in some manner associated with coronary vasoconstriction in preclinical heart disease. Thompson considered this possibility.

In a similar manner Katz[17] and McGuire[18] have observed reversible T-wave changes in nervous individuals. Graybiel, Starr, and White[19] have also noted S-T interval and T-wave changes resulting from the inhalation of tobacco smoke. The T-wave inversions following the ingestion of ice water are well known.

On the whole, however, the number of adults exhibiting T-wave inversion in the precordial leads in the absence of demonstrable heart disease is comparatively small.

In reviewing over 3,000 electrocardiograms made during a one-year period at an Army installation, a small number of T_4 inversions was noted. But, with three exceptions, these were all associated with organic disease of the heart and/or pericardium or occurred during the course of acute rheumatic fever. The three exceptions were extensively studied, but no evidence of heart disease was ever demonstrated. All three exceptions were in Negroes. This observation suggested a preponderance of the anomaly among Negroes, and since a review of the literature failed to reveal any large scale study of electrocardiograms of normal adult or juvenile Negroes, such a survey was undertaken.

MATERIAL AND METHODS

The instruments used in this study were Sanborn cardiettes which were frequently calibrated and compared. All tracings were made with the subject

TABLE I. PHYSICAL DESCRIPTION, HISTORY, AND LABORATORY FINDINGS IN SUBJECTS WHO DEMONSTRATED T_4 ABNORMALITY

AGE (YR.)	SEX	HEIGHT IN INCHES	WEIGHT IN POUNDS	USE OF DRUGS	HISTORY OF RECENT ILLNESS	HISTORY OF RHEUMATIC FEVER	HISTORY OF SCARLET FEVER	KAHN REACTION	HEMOGLOBIN	SEDIMENTATION RATE MM./HR.*	SICKLE CELLS	HEART SIZE DEVIATION BY X-RAY†	BLOOD PRESSURE	PHYSICAL EXAMINATION
32	F	63	148	0	0	0	0	–	81	13	0	0	116/72	Negative
26	F	64	138	0	0	0	0	–	98	11	0	0	118/76	Negative
23	F	64	150	0	0	0	0	–	73	13	0	− 4%	108/80	Negative
23	F	67	146	0	0	0	0	–	78	12	0	− 7%	116/70	Negative
24	F	63	135	0	0	0	0	–	86	14	0	− 3%	110/74	Negative
23	F	62	132	0	0	0	0	–	82	6	0	− 9%	116/74	Negative
18	F	68	133	0	0	0	0	–	96	12	0	0	100/70	Soft systolic basal murmur
21	F	60	117	0	0	0	0	–	82	10	0	−12%	110/78	Soft systolic basal murmur
32	M	69	148	0	0	0	0	–	98	2	0	−16%	108/7[illegible]	Negative
23	M	68	135	0	0	0	0	–	90	11	0	− 4%	110/75	Negative
24	M	69	140	0	0	0	0	–	104	4	0	− 9%	120/80	Negative

*Erythrocyte sedimentation rate determined by modified Cutler method; normal for men: 0 to 10; for women, 0 to 15.
†Percentage of heart size deviation from average normal according to Ungerleider tables.

lying down on a padded wooden table. Occasionally, when abnormalities were observed, the electrocardiogram was repeated in the erect position. Particular care was taken in the recording and development of the tracings, and most of this was done by the author. All of the subjects were adults between the ages of 18 and 35 years. There were 200 Negro men, 100 Negro women, 100 white men, and 100 white women. They were picked from the normal active personnel of an Army post, and no hospital patients were included. No one was included who had had a recent illness, a history of gonorrhea or syphilitic infection, or any complaints referable to the cardiovascular system. All subjects were told about the study in a general way and were reassured before the electrocardiograms were made. Each was rested for ten minutes to one hour. When asked to return for additional studies, they were once more assured that no heart disease was present and that they had no cause for concern.

Routine four-lead electrocardiograms (Leads I, II, III, and IV F) were made and examined. All subjects who showed any degree of T_4 inversion were requested to return for further testing. At this time, a careful history was obtained with particular reference to rheumatic fever, scarlet fever, recent pharyngitis, cardiovascular symptoms, and the use of any drugs. The temperature, weight, and height were recorded. The blood pressure was measured, and the heart was carefully examined. The following additional studies were obtained: (1) teleroentgenogram of the chest, (2) hemoglobin, (3) Kahn reaction, (4) examination of the blood film for sickling, and (5) sedimentation rate. Another electrocardiogram was then made, employing, in addition to the original four leads, the six standard precordial leads with the indifferent electrode on the left leg. In some cases Leads IV R, IV L, and IV V were also recorded.

Table I summarizes the physical descriptions and laboratory findings in those subjects who showed T-wave abnormalities and were studied sufficiently to be included. Three subjects were omitted from this list because of incomplete records.

RESULTS

The results of this study are summarized in Table II. It will be noted that, of the 300 Negroes studied, 4.6 per cent had tracings which would be considered abnormal. The women had a much larger incidence of T-wave abnormality: 4 per cent were diphasic, and 4 per cent were inverted. All of the abnormal tracings obtained from the women are reproduced in Figs. 1 and 2. The incidence of T-wave changes in the precordial leads of Negro men was 3 per cent while 1 per cent had frankly abnormal curves. The latter are reproduced in Figs. 3 and 4; those showing merely diphasic T waves are not shown. An electrocardiogram was obtained from one white man in which the T waves in the precordial leads were diphasic with the negative portion 0.5 mm. in depth. There were no abnormal tracings among the white women.

Table III is a summarized analysis of the records. Since it is not apparent from the tracings shown, it is well to add that the heart rates varied between 64 and 90 and there were no instances of abnormal arrhythmia. Several general impressions are possible from examination of the electrocardiograms. There

were no instances of abnormality of any portions of the curves derived from the limb leads. The axis varied between +33 and +103, i. e., normal to very slight right axis deviation; no instance of left axis deviation was noted. T_1 and T_2 were always upright and an inverse relationship apparently existed between T_2 and T_4; the greater the height of T_2, the greater the depth of T_4. T_3 was never frankly inverted but was flat in two instances and diphasic in one. All of the precordial T waves were diphasic or negative from Lead CF_1 through Lead CF_4; Leads CF_1 and CF_2 usually had the greatest negativity and Lead CF_4 had the least. In some instances, inversion was present in Lead CF_5 and even in CF_6, but, for the most part, the T waves in Leads CF_5 and CF_6 were upright. Where Lead CR (IV R) was made, the T waves were usually but not invariably upright. Leads IV L and IV V were variable.

TABLE II. SUMMARY OF THE FREQUENCY OF ABNORMAL PRECORDIAL T WAVES IN 300 ADULT NEGRO AND 200 WHITE SUBJECTS

Negro, both sexes (300)		
Normal curves	286	95.34%
Diphasic T_4	8	2.66%
Inverted T_4	6	2.00%
Negro men (200)		
Normal curves	194	
Diphasic T_4	4	
Inverted T_4	2	
Negro Women (100)		
Normal curves	92	
Diphasic T_4	4	
Inverted T_4	4	
Whites, both sexes (200)		
Normal curves	199	99.5%
Diphasic T_4	1	00.5%
Inverted T_4	0	00.0%
White men (100)		
Normal curves	99	
Diphasic T_4	1	
White Women (100)		
Normal curves	100	

Approximately two months after the original tracings were obtained, those subjects who exhibited electrocardiographic abnormalities were requested to return for additional studies. All of the women and four of the men were reached, but the remainder had left the post and could not be re-examined. Of the electrocardiograms which were reported, six remained unchanged (*B* and *C* in Fig. 1, *G* and *H* in Fig. 2, Fig. 3, and one electrocardiogram not shown). *A* in Fig. 1 had become entirely normal. *D* retained an inverted T wave in Lead CF_2 but the T wave in Lead CF_3 had become diphasic and that in Lead CF_4 had become upright. In *E*, the T wave in Lead CF_5 became upright and in Leads CF_3 and CF_4 it was diphasic with Lead CF_2 unchanged. In *F*, the T wave in Lead CF_4 became positive, in Lead CF_3 it became flat, and in Lead CF_2 there was no change. One of the tracings, that of a Negro man, which demonstrated diphasic T waves, became

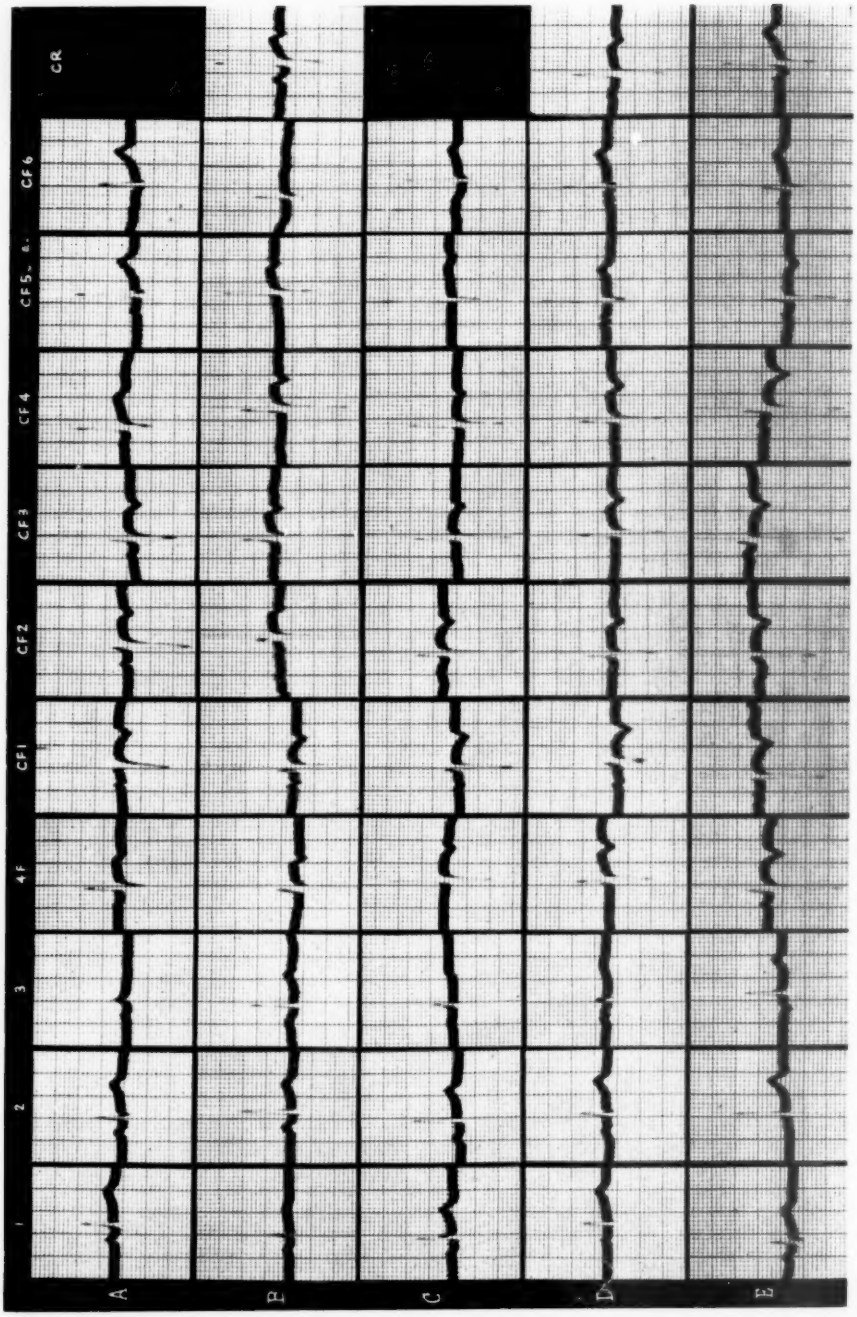

Fig. 1.—Abnormal electrocardiograms of five Negro women.

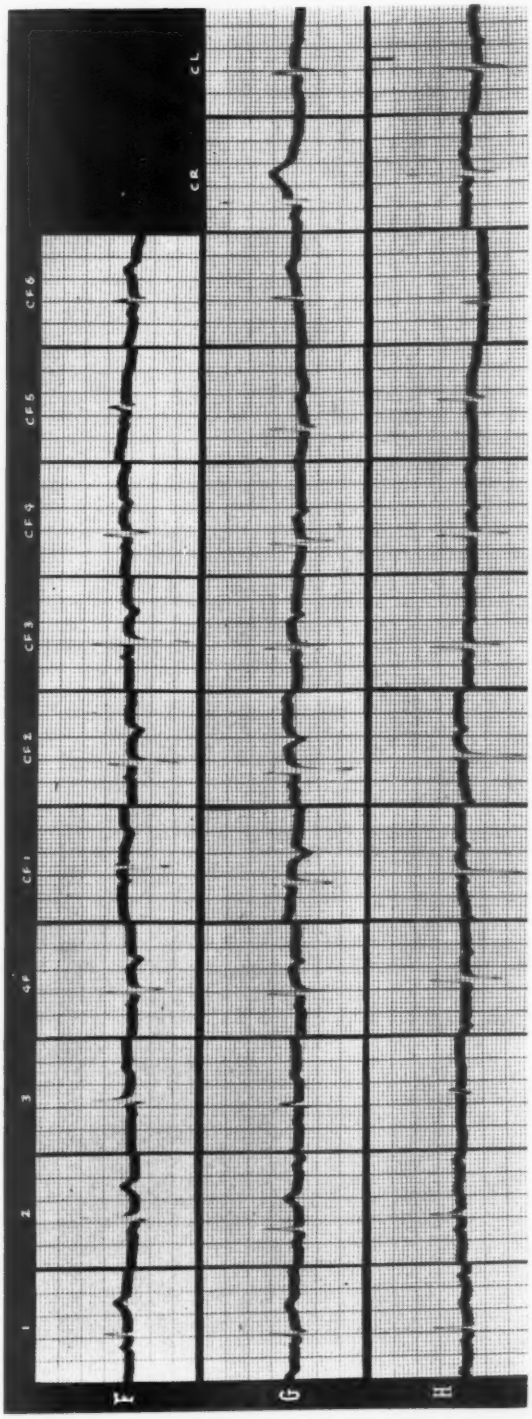

Fig. 2.—Abnormal electrocardiograms of three Negro women.

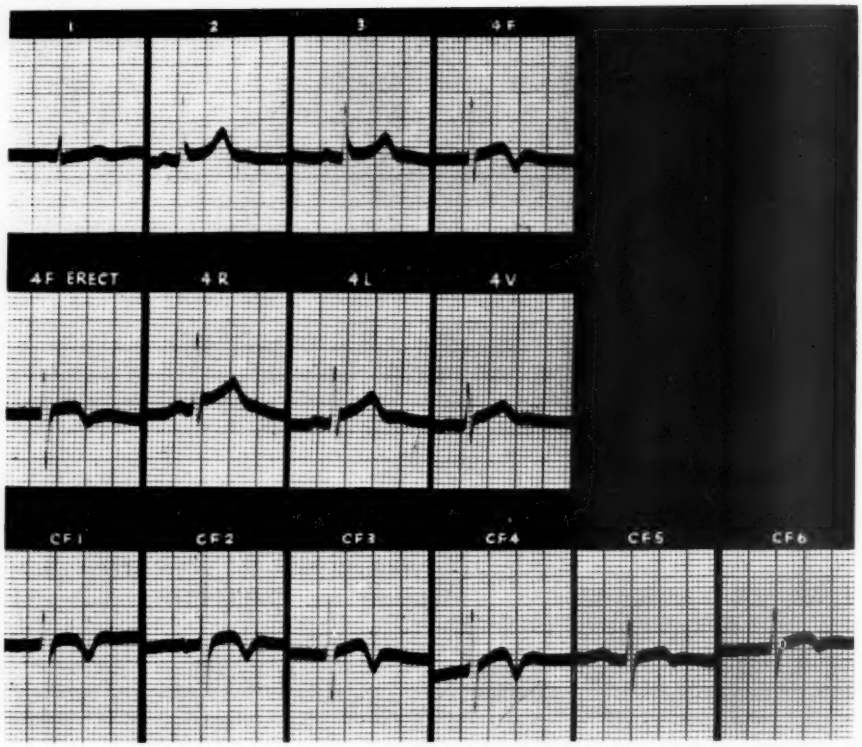

Fig. 3.—Abnormal electrocardiograms of a Negro man.

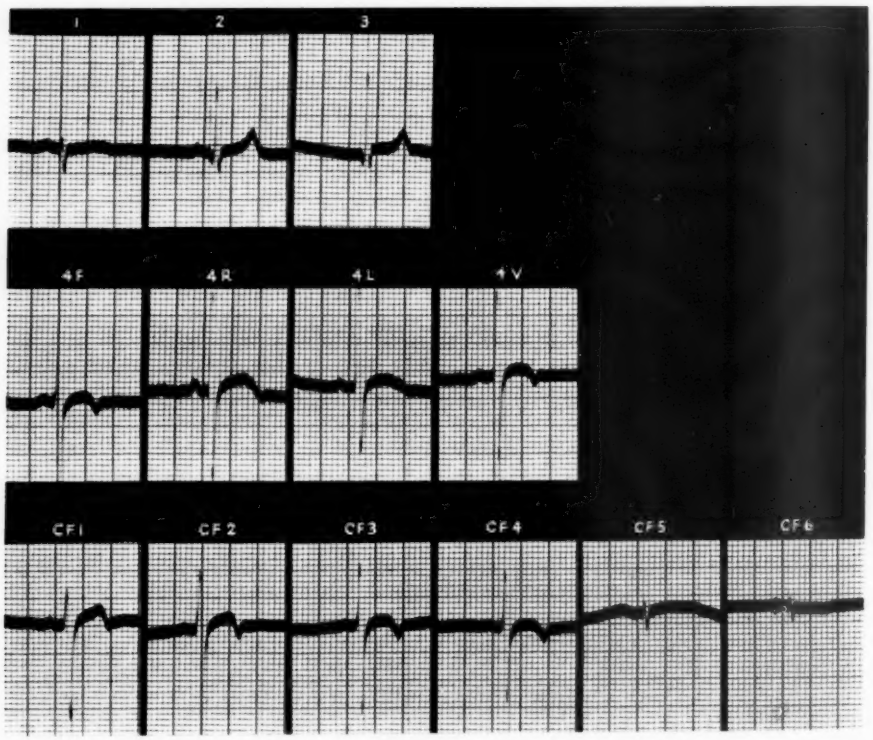

Fig. 4.—Abnormal electrocardiogram of a Negro man.

TABLE III. SUMMARY OF RECORD ANALYSIS*

RECORD DESIGNATION	P-R INTERVAL	QRS DURATION	AXIS	T_1	T_2	T_3	T_4 (IV F)	T_5-CF_1	T-CF_2	T-CF_3	T-CF_4	T-CF_5	-CF_6	T-IV R	T-IV L
A	0.14	0.09	+37	+1.	+1.5	0.0	+1.0 −1.0	−2.0	−1.5	−1.8	+2.0 −0.5	+3 0	+2.5		
B	0.14	0.08	+73	+0.5	+1.5	+1.0	+1.2 −0.5	−1 5	+1.0 −0.5	+1.0 −1.0	+1.0 −1.5	+0.5 −0.5	+0.5	+1.0 −1.0	
C	0.18	0.06	+43	+2.0	+2.0	0.0	−1.5	−2.0	−1.5	−1.0	−1.0	+0.5 −0.	+1.5		
D	0.18	0.08	+33	+1.5	+0.2	+0.5	+0.5 −1.5	−3.0	−2.0	−2.0	−2.0	+1.5	+2.0	+0.5 −1.5	
E	0.1[illegible]	0.06	+62	+1.5	+3.0	+1.5	−3.0	−2.5	−2.5	−2.5	−3.3	−1.5	+1.5	+2.2	
F	0.12	0.10	+58	+2.0	+2.3	+0.5	−1.6	−1.5	−2.0	−1.4	+0.5	+0.	+1.5		
G	0.15	0.06	+47	+1.5	+2.5	+1.0	+0.5 −1.0	−3.0	−3.0	−1.9	+0.5 −1.0	+1.0 −1.0	+1.3	+3.0	−0.5
H	0.14	0.08	+34	+1.0	+0.5	−0.3 +0.2	−1.0	−1.2	−1.0	−1.0	−1.0	+0.5	+0.5	+1.0 −0.5	−1.0
Fig. 3	0.14	0.09	+87	+0.1	+4.0	+3.0	−3.0	−3.0	−3.5	−3.0	−3.0	+1.0 −0.5	+1.0 −0.5	+3.0	+3.0
Fig. 4	0.12	0.09	+103	+0.5	+3.5	+3.0	−2.0	+2.0 −0.5	+1.0 −1.0	−1.5	−1.5	+1.0	0.0	+2.0	+1.0

*T-wave height expressed in millimeters.

entirely normal while another developed frankly inverted T waves. It would appear, therefore, that when changes in the direction of normal become manifest they do so first in those leads farthest from the sternum. In addition, it is probable that changes may occur either toward or away from the normal pattern.

DISCUSSION

The size of the group being studied is too small for detailed statistical conclusions. However, certain facts are evident. T wave inversion in the precordial leads is far more common among normal adult Negroes than among white subjects and is apparently more frequent in Negro women than in Negro men. In no case here reported was there any cardiovascular complaint or any demonstrable evidence of organic or functional disease of the heart. None of the subjects had any active or recent infection. The abnormalities were noted in a group of healthy, confident, young men and women who had not been smoking, taking drugs, drinking cold water, or hyperventilating.

In a general way, it is noted that in the cases reported in this study, the heart tended to be relatively small and there were no instances of enlargement. Similarly, the electrical axis fell toward the right and was never rotated to the left. Although a few of the women were rather stout, none was obese and most of the chests were thin. The men, particularly, were thin chested. These observations tend to confirm the impression of juvenile chest configuration in these individuals.

In the literature reviewed it is probable that the studies were carried out on white subjects. References to electrocardiographic studies on the Negro are limited. Laws,[20] in a discussion of the etiology of heart disease in the Negro, concludes that "The Negro develops heart disease at an earlier age, on the average, than the white." Is it likely that the Negro subjects under discussion were demonstrating the first evidence of organic heart disease? Observations incident to the present study argue against such a conclusion. It is also thought that certain degenerative cardiac conditions, angina pectoris, for example, occur less frequently in Negro than in white subjects. Weiss[21] has reported, however, that angina in Negroes is fairly common. Ashman,[22] who made an electrocardiographic study of Caucasians and Negroes, reported no unusual incidence of T-wave abnormality. Furthermore, all of his subjects were over 30 years of age and the data were obtained from hospital records. Presumably, these were all cardiac patients since there was a high incidence of organic heart disease.

Apparent inadequacies of the literature are noted. At the present time, no comparative studies can be found on white and Negro children. It is known that most white children have acquired an upright T wave in the chest lead by the age of 15 years. Can the same be said about the Negro? Comparatively few studies have been recorded regarding the manner in which the T wave becomes upright during adolescence. Does it become positive first in the fifth or sixth precordial position, as seems probable, or are the changes first apparent in other positions? Is the progress from the negative to the positive direction

constant and steady, or is it subject to frequent recessions? The work of Robinow and his associates[10] suggests that the latter is actually the case.

It is possible that not all cases of T_4 inversion in the group herein reported were due to the same cause. It will be recalled that of 12 subjects who were reexamined after approximately ten weeks, five showed changes toward the normal. It would be altogether too fortuitous to expect that so high a proportion should have chosen the same time to acquire adult characteristics. However, since it is uncertain that the erection of a juvenile T wave is a continuous progression and not an unsteady equilibrium, that possibility must be considered. Unfortunately, because of the constantly changing character of the personnel on an Army post, it was not possible to repeat the studies on the same group.

There exists, therefore, an apparent abnormality, possibly transient or shifting in character, in a very appreciable percentage of young and presumably healthy Negro men and women. It is more common in women than in men and apparently occurs very rarely in white subjects. It is associated with suggestive juvenile characteristics. Women's chests are normally less broad from side to side than men's and this may account for the higher incidence observed in the female sex.

These findings were noted in the complete absence of symptoms or signs of organic or functional heart disease. In a similar manner, there was no evidence of current or recent infection, rheumatic fever, drugs, syphilis, anemia, or sickling of erythrocytes. The reasons noted and the exclusion of other known causes of such anomalies lead to the conclusion that the T-wave inversion in the chest leads of otherwise normal adults constitutes a persistence of the juvenile pattern and should be considered a normal variant.

Since this anomaly is manifested more frequently when the left leg rather than the right arm is employed for the indifferent electrode, it is desirable that the study be repeated using various indifferent connections. Electrocardiograms should also be made over a prolonged period of time, as the phenomenon apparently disappears with the passage of time.

Much additional study of the electrocardiograms of youthful white and Negro subjects will be required before a satisfactory explanation of this apparent anomaly can be made. At the present time, there seems to be no adequate reason for the greater frequently of juvenile electrocardiograms in adult Negroes than in adult white subjects.

SUMMARY

1. In an electrocardiographic survey of 500 healthy adults, 300 Negro and 200 white subjects, diphasic or inverted T waves in the precordial leads were observed in 14 Negroes, eight among 100 women and six among 200 men. Among white subjects a diphasic T wave was noted in only one instance.

2. It is suggested that the presence of diphasic or inverted T waves in the precordial leads under the circumstances constituted a persistence of the juvenile pattern and was not a manifestation of organic heart disease.

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ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING UPPER RESPIRATORY INFECTIONS

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IT IS becoming increasingly apparent that transient or permanent cardiac involvement as a result of a toxic state or direct bacterial or viral invasion may be a concomitant of many infectious diseases.[1-4] The following report is presented to demonstrate cardiac susceptibility in the course of mild, apparently benign upper respiratory infection, in many instances with no bacteriologic evidence of pathogenic microorganisms in the nasopharyngeal secretions.

MATERIAL AND METHODS

The thirteen patients presented in this series were all military personnel, hospitalized because of respiratory infection. Cultures were made routinely from swabbings of the nasopharynx. Serial electrocardiograms at two- or three-day intervals, usually starting on the day after admission, and repeated cardiac fluoroscopic and clinical examinations were made.

RESULTS

The clinical and laboratory data are shown in Table I. Of the thirteen cases, Group A beta hemolytic streptococci were present in nasopharyngeal cultures in only five. Only one type was recovered on repeated culture from each of these five cases. In one case a Group B and in one a Group G beta hemolytic streptococcus was isolated. In six cases, a beta hemolytic streptococcus was at no time discovered in the nasopharynx, repeated cultures showing only the usual nasopharyngeal organisms.

The most frequent electrocardiographic changes obtained were T-wave inversions and depressions. These occurred as the only change in seven cases. Four patients developed auriculoventricular conduction disturbances with prolongation of the P-R interval from 0.04 to 0.05 second beyond the normal duration. One additional patient showed marked T-wave changes and an intermittent A-V nodal rhythm. One patient also showed a widening of the QRS complex and runs of A-V nodal tachycardia. T-wave changes and the variation of the P-R interval cannot be ascribed to postural effects, for all electrocardiograms were taken with the patients in the recumbent position.

Clinically, except for Case 5, these patients were not acutely ill on admission nor during their period of hospitalization. There was no essential difference in the severity or duration of the acute phase between those with a hemolytic

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TABLE I. CLINICAL AND LABORATORY DATA ON THIRTEEN CASES OF UPPER RESPIRATORY INFECTION

CASE	AGE	DIAGNOSIS	ECG CHANGE (T WAVES IN MM.; P-R AND QRS IN SEC.)	DAYS INFECTION PRESENT BEFORE ECG CHANGE	DURATION OF ECG CHANGE (DAYS)	THROAT CULTURE (BETA HEMOLYTIC STREPTOCOCCUS)	OTHER LABORATORY DATA		REMARKS
							WHITE BLOOD CELLS*†	ERYTHROCYTE SEDIMENTATION RATE (WESTERGREN)	
1	21	Acute tonsillitis	T_1, +1.0 to +1.5 T_2, +1.0 to +2.0 T_3, Semi-inverted to +1	19	10	0	10,200, P 84	1 mm.	First admission
		Acute tonsillitis	T_1, +0.5 to +1.2 to +1.2 T_2, +0.5 to −1.5 to +1.0 T_3, −1.0 to −2.0 to semi-inv. T_4, +2.0 to 0.0 to +3.5	5	41	Group A —not typable	19,000, P 88	81 mm.	Second admission, 5 months later; received 15 Gm. sulfadiazine
2	20	Acute tonsillitis	P-R, 0.21 to 0.16	11	9	0	9,950, P 61	50 mm.	
3	23	Acute nasopharyngitis	T_1, +1.0 to 0.0 T_4, +2.2 to −1.0	5	83	0	5,100, P 53	6 mm.	
4	19	Acute nasopharyngitis	P-R, 0.20 to 0.16	3	7	0	5,000, P 54	18 mm.	
5	28	Acute tonsillitis	T_1, +3.0 to +3.5 T_2, +1.5 to −1.3 T_3, −3.0 to −3.5 T_4, +8.5 to 13.5	28	74	Group A, Type 12	19,500, P 90	28 mm.	Received 54 Gm. sulfadiazine
6	32	Acute tonsillitis	T_1, 0.0 to +1.0 T_2, − 1.0 to +0.5 T_3, − 2.0 to −1.0 T_4, +2.0 to +2.5 Intermittent A-V nodal rhythm	8	72	Group B	6,300, P 71	46 mm.	Received 20 Gm. sulfadiazine

7	25	Acute tonsillitis	T_1, +0.5 to +2.0 T_2, +0.5 to +1.5 T_3, 0.0 to +0.5 T_4, +0.5 to +2.5	8	10	Group A, Type 41	15,200, P 92		Received 15 Gm. sulfadiazine
8	29	Acute nasopharyngitis	QRS, 0.12 to 0.10 Runs of A-V nodal tachycardia	6	24	0	6,100, P 63		
9	18	Acute tonsillitis	T_1, +1.0 to +2.0 T_2, +1.5 to +2.7 T_4, −2.0 to +3.0	10	8	Group G	5,600, P. 53	3 mm.	
10	23	Infectious mononucleosis	P-R, 0.16 to 0.20	26	12	Group A, Type 12	8,200, L 54 (many atypical)	22 mm.	Heterophile, +1:3584
11	21	Acute nasopharyngitis	P-R, 0.22 to 0.17	3	5	0	4,200, P 64		
12	20	Acute nasopharyngitis	T_1, Semi-inverted to +2.5 T_2, +2.5 to +2.7 T_3, +2.5 to +1.0 T_4, +2.5 to +8.0	5	7	0	5,600, P 70	12 mm.	
13	20	Infectious mononucleosis	T_1, +0.5 to +1.0 T_2, +1.5 to +3.0 T_3, +0.8 to +2.0 T_4 +1.0 to +3.0	6	12	Group A, Type 36	6,300, L 74 (one-third atypical)	10 mm.	Heterophile, +1:56; received 78 Gm. sulfadiazine

*Polymorphonuclears.
†Lymphocytes.

streptococcal infection of the throat and those with a simple nasopharyngitis. A leucocytosis was present in three of the patients with Group A infection but in none of the others. The erythrocyte sedimentation rate was not elevated in all cases. Two of the patients with Group A hemolytic streptococci in the nasopharynx clinically and hematologically had infectious mononucleosis.

None of these patients had a past history suggestive of rheumatic fever. None showed clinical or fluoroscopic evidence of pre-existing cardiac disease nor did they develop any clinical signs or symptoms of heart disease, other than the electrocardiographic changes, during the period of observation. There was no laboratory evidence of a renewed active infectious process during the period that electrocardiographic changes were present.

Only one patient developed clinical manifestations suggesting rheumatic fever (Case 10). This patient suffered from fairly severe arthralgias for one week during his illness, but there were no objective signs of joint involvement. He had a typical infectious mononucleosis with a heterophile agglutination titer of 1:3,584.

In a fruitless attempt to eliminate the hemolytic streptococcus from the nasopharynx, five patients in this series (Table I, Cases 1, 5, 6, 7, and 13) were given sulfadiazine in varying doses. In these five the drug was started two, twenty-eight, one, four, and ten days, respectively, prior to the first electrocardiographic indication of myocardial involvement. All other patients received only symptomatic treatment during the acute phase.

CASE REPORTS

CASE 1.—This case is of considerable interest in that the patient was hospitalized twice with acute tonsillitis and on each admission developed electrocardiographic changes despite a distinct difference in the nasopharyngeal cultures. The first admission was because of a progressively severe sore throat of one week's duration. The oral temperature was 101° F. and examination revealed diffuse injection of the pharynx; the tonsils were large and inflamed. The throat culture showed no unusual organisms. Treatment was entirely symptomatic. Signs and symptoms rapidly subsided and the temperature returned to normal on the fifth hospital day. Electrocardiographic evidence of myocardial involvement, manifested by low T waves in Leads I and II and inversion of the T wave in Lead III, appeared on the nineteenth day of illness. Three days later the tracing had returned to normal (Fig. 1, *A* and *B*).

The patient was well at time of discharge from the hospital and remained so until five months later when he was readmitted because of sore throat, malaise, and fever of one day's duration. The tonsils were large, reddened, and covered with exudate. The oral temperature was 103° F. and remained elevated for the first four hospital days. Throat culture revealed a Group A beta hemolytic streptococcus which was not typable. On the fifth day of illness, significant changes were present in the T waves of the electrocardiogram. These changes became progressively more marked, and the tracing did not return to normal until forty-one days later (Fig. 1, *C*, *D*, and *E*). During this period the patient was objectively and subjectively well; laboratory data revealed no evidence of infection after the tonsillitis had subsided. Subsequent follow-up for two months after discharge from the hospital revealed no clinical or laboratory abnormalities.

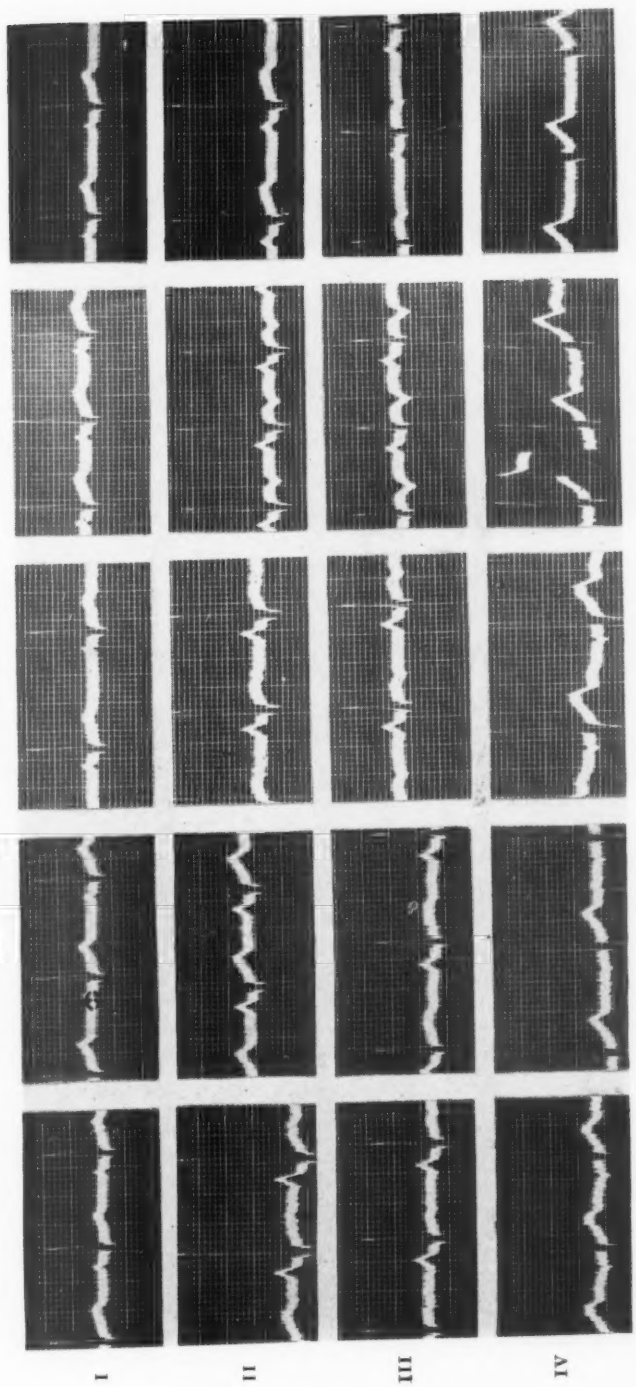

Fig. 1.—Case 1. Electrocardiograms *A* and *B* taken nineteen and twenty-two days, respectively, after onset of acute tonsillitis. *C*, *D*, and *E* taken five, twelve, and forty-one days, respectively, after onset of similar illness five months later.

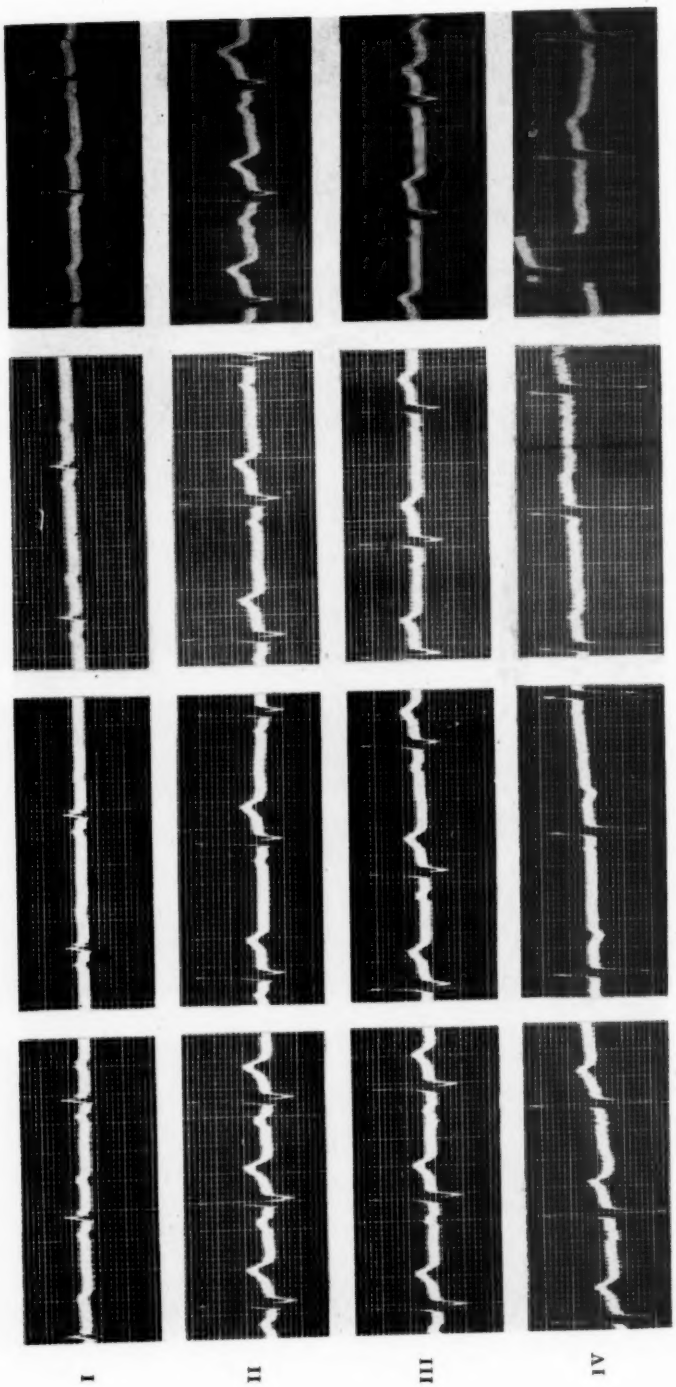

Fig. 2.—Case 3. Electrocardiograms *A*, *B*, *C*, and *D* taken two, five, twenty, and eighty-three days, respectively, after onset of acute nasopharyngitis.

Two other cases illustrating the development of marked electrocardiographic changes early in the course of simple upper respiratory infections are presented.

CASE 3.—W. C. was hospitalized because of cough, fever, and chilliness of two days' duration. The temperature was 100° F. orally on admission, and although the patient appeared moderately ill, the only abnormal finding was congestion of the nasal mucosa. Laboratory data were normal. Repeated nasopharyngeal cultures failed to show any unusual organisms. The patient was afebrile after the first hospital day and all signs and symptoms were gone in four days. At no time was there a leucocytosis or elevation of the erythrocyte sedimentation rate. During a five-month period of observation he displayed no clinical cardiovascular signs or symptoms.

The electrocardiogram on the fifth day of illness revealed an almost isoelectric T wave in Lead I and an inverted T wave in Lead IV (Fig. 2, *A* and *B*). Twenty days later T_1 measured 1 mm. and T_4 was slightly upright (Fig. 2. *C*). The first normal tracing was obtained eighty-three days after the onset of the upper respiratory infection (Fig. 2, *D*); subsequent electrocardiograms showed no further change.

CASE 9.—S. C., an 18-year-old soldier, was admitted to the hospital because of a slight nonproductive cough and sore throat of three days' duration. Examination revealed moderate swelling and redness of the tonsils with flecks of white exudate on the surface. The patient was not acutely ill and was afebrile on admission and remained so throughout his hospital stay. The acute manifestations subsided in three days.

Laboratory data were normal and did not change significantly during the period of hospitalization. A Group G beta hemolytic streptococcus was obtained on initial throat culture and was present on repreated nasopharyngeal swabbings. No other beta hemolytic streptococci were obtained.

The electrocardiogram taken ten days after the onset of the patient's upper respiratory infection showed a deeply inverted T wave in the fourth lead. Two days later T_4 was upright but the T waves in the first three leads were distinctly lower. One week later the T waves were normal in all leads and subsequent follow-up studies revealed no change (Fig. 3, *A*, *B*, and *C*).

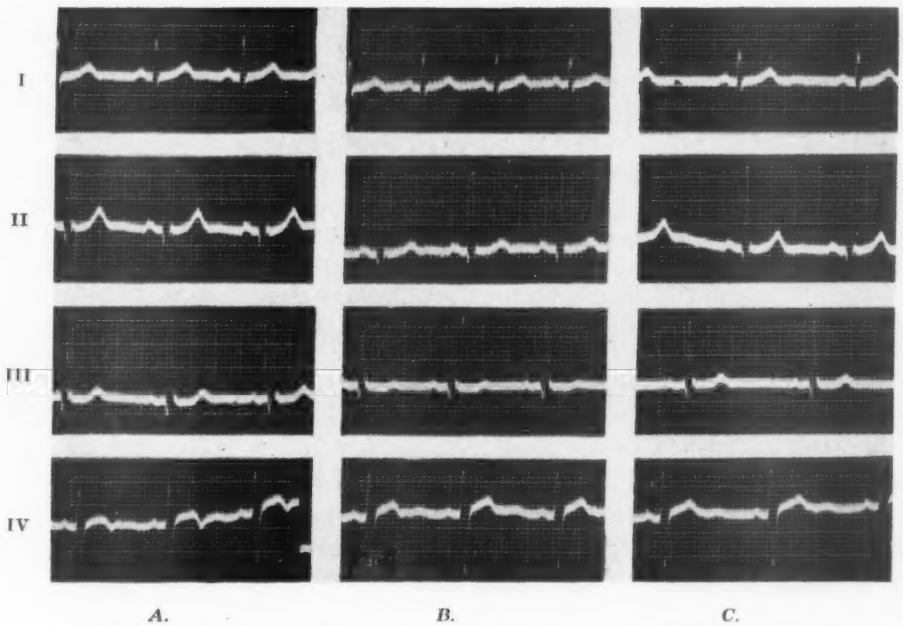

Fig. 3.—Case 9. Electrocardiograms *A*, *B*, and *C* taken ten, twelve, and nineteen days, respectively, after onset of acute tonsillitis.

DISCUSSION

The electrocardiographic changes found in these thirteen patients are unequivocal evidence of myocardial involvement. Since all patients recovered, the exact pathologic significance of the electrocardiographic changes can only be surmised. Candel and Wheelock[3] recently reported a case of sudden death in a patient with acute suppurative tonsillitis from whom throat cultures had shown a beta hemolytic streptococcus (not grouped). Microscopically the myocardium showed pronounced fragmentation of the bundles with loss of cross striations, disintegration of muscle nuclei, interstitial edema, and a widespread diffuse infiltration of the interstitial tissue by polymorphonuclear cells. This apparently is the first recorded post-mortem report of acute nonspecific myocarditis following acute tonsillitis, although Schultz,[5] in 1937, recorded a case of sudden death in a 21-year-old soldier in whom autopsy revealed a diffuse interstitial myocarditis believed to have been secondary to tonsillar infection.

Several authors have reported electrocardiographic evidence of acute myocarditis following tonsillitis. Scherf[6] demonstrated five such cases and indicated that from 10 to 15 per cent of patients with acute tonsillitis develop signs, symptoms, or changes in the electrocardiogram suggesting myocardial involvement. Carr and Walsh[7] and Maher and Wosika[8] have also recorded electrocardiographic changes with tonsillar infection. In their paper on acute nonspecific myocarditis, Candel and Wheelock[3] included a case of peritonsillar abscess and one of infectious mononucleosis.

It is quite possible that electrocardiographic changes occur in much greater frequency in all respiratory infections than has been previously recognized. Scherf and Boyd[9] suggest that with the frequency of infectious diseases and miscellaneous infections such as tonsillitis, there are but few individuals who at some time do not have small inflammatory myocardial foci. To date, however, since no serial electrocardiographic study has been made in a large series of patients with upper respiratory infection, an accurate statistical incidence of evidence of cardiac involvement in this type of illness has not been obtained.

Unfortunately the bacteriologic findings in the nasopharynx were not correlated with the evidence of myocardial involvement in previously reported cases. This may be of extreme importance in an attempt to evaluate the immediate significance of the electrocardiographic changes as well as the future outlook for the patient in view of the opinion recently expressed by Rantz, Boisvert, and Spink.[10]

These authors obtained electrocardiographic evidence of carditis similar to that described here in 10.8 per cent (twenty cases) of 185 patients on whom serial electrocardiograms were taken during and following Group A beta hemolytic streptococcal throat infections. A true latent period between recovery from the sore throat and the development of changes in the electrocardiogram occurred in only six of these patients. When a latent period was demonstrated, reinfection by a new type of Group A streptococcus had frequently taken place.

Because carditis was not demonstrable in 80 per cent of their series, a toxic etiology for the carditis in the group with no latent period was rejected. Pre-

viously unrecognized streptococcic respiratory infection with the establishment of an abnormal tissue sensitivity was postulated as the mechanism for the pathogenesis of the myocardial involvement in these patients. In those patients in whom a latent period between the respiratory infection and carditis occurred, the same mechanism was considered responsible because a new type of Group A streptococcus was discovered in the throat on subsequent cultures. Thus these authors suggested grouping cases of carditis with and without a latent period following the acute respiratory phase, rheumatic fever, and postscarlatinal arthritis under the term "poststreptococcic state."

If one is inclined to accept this attractive hypothesis, then the electrocardiographic changes demonstrated at least in some of the thirteen patients in the present study assume an even greater potential significance. Five of these patients repeatedly showed a Group A hemolytic streptococcus in the nasopharynx during the acute phase and during convalescence. Of these five, two patients had definite infectious mononucleosis. Although a study previously carried out at this hospital demonstrated a Group A carrier rate of only 1.9 per cent in this geographic area[11] it is quite possible that the organisms were not responsible for the disease process in the two patients with infectious mononucleosis and that they were merely carriers of the hemolytic streptococcus. A Group B hemolytic streptococcus was isolated in one case. This organism is not infrequently found in the upper respiratory tract and is usually not pathogenic for man. In one case a Group G streptococcus was repeatedly isolated. This type may at times be of clinical significance.

Granting that five and possibly seven cases were actually infected with hemolytic streptococci, it is to be noted that comparable electrocardiographic changes occurred in six patients from whose throats at no time unusual organisms were isolated. This certainly suggests a nonspecific toxic process as the causative mechanism and can just as readily be applied to those cases in which pathogenic organisms were demonstrated as can the theory of specific sensitization of the myocardium by products of the hemolytic streptococcus.

In regard to the "streptococcal group" of cases, and perhaps even in the others, the mechanism of the production of carditis is of more than academic importance. Neither the study by Rantz, Boisvert, and Spink[10] nor this study reveals the eventual outcome in such patients. It is well known that signs of valvular disease may not appear for a considerable period of time after all evidence of rheumatic fever has subsided. Many studies have also shown that in from 25 to 50 per cent of patients in whom rheumatic heart disease is found, no antecedent history of rheumatic fever can be obtained. Thus, if such patients who demonstrate evidence of carditis during respiratory infection without other accepted criteria of rheumatic fever[12] are considered to be in the same group as those with the "rheumatic state," then prognosis in such patients must be guarded, and certainly every effort must be made to prevent recurrent respiratory infection in such individuals. If, on the other hand, the underlying mechanism is considered to be of nonspecific "toxic" origin and not related to a "rheumatic" sensitization of cardiac tissue, then the possibility of progressive or future cardiac

damage is considerably reduced and electrocardiographic changes assume much less importance.

Upper respiratory infection has been at times cited as the cause of Fiedler's or diffuse isolated myocarditis.[1] Hansmann and Schenken[13] suggest that the microscopic appearance of the muscle fibers in isolated myocarditis makes one suspect that the same thing occurs in the milder forms of toxic myocarditis from which patients usually recover without clinical recognition. Thus transient electrocardiographic changes occurring in upper respiratory infections would be considered to represent a *forme fruste* of acute diffuse myocarditis.

Candel and Wheelock[3] suggest this same possibility in discussing acute myocarditis following tonsillitis. They also speak of permanent abnormal electrocardiographic alteration. However, it would seem that in view of changes in four of our cases persisting for forty-one, eighty-three, seventy-four, and seventy-two days, respectively, before returning to normal, it is dangerous to conclude without a long follow-up period that permanent changes have resulted.

While it is most likely that the electrocardiographic changes in those patients who received sulfadiazine in an attempt to eliminate the hemolytic streptococcus from the nasopharynx were due to the respiratory infection, in view of recent necropsy and experimental evidence of myocardial involvement due to sulfonamide administration,[14-22] this drug cannot be entirely excluded as an etiologic factor. Electrocardiographic evidence of myocardial involvement due to sulfonamides alone has recently been obtained on six patients. This study will form the basis of a subsequent report. In this particular series, however, the drug may at best be considered an additive toxic factor rather than the sole responsible one for the electrocardiographic changes.

It is important to note that in none of these thirteen patients did cardiac signs or symptoms develop during the period when the electrocardiogram indicated myocardial involvement. This is in marked contrast with the experience of Scherf,[6] who described weakness, palpitation, slight dyspnea, precordial or substernal pain, apprehension, tachycardia, and, in more severe cases, cardiac enlargement, gallop rhythm, and rarely congestive failure as occurring from one to two days after the onset of acute tonsillitis or shortly after the acute respiratory phase had subsided. The discrepancy between these two reports may possibly be attributed to the fact that our patients were all previously healthy individuals with greater cardiac reserve. It is apparent that on the basis of the clinical manifestations of the thirteen patients in this study, myocardial involvement would not have been suspected, so that the present report can offer no indications as to when or in which particular patients with upper respiratory infection serial electrocardiographic studies should be made.

SUMMARY AND CONCLUSIONS

1. Thirteen cases of upper respiratory infection in which electrocardiographic evidence of myocardial involvement was obtained are presented. Group A beta hemolytic streptococci were isolated on throat culture from only five of these thirteen patients.

2. The demonstration of comparable electrocardiographic changes in patients with and without hemolytic streptococcal respiratory infection favors a nonspecific toxic etiology as the underlying mechanism for both rather than the theory of streptoccocal "rheumatic" sensitization of the myocardium.

3. Whether or not such cases represent a *forme fruste* of Fiedler's myocarditis can only be speculated upon, but this possibility is worthy of serious consideration.

4. The possible relation of sulfonamide administration to the development of myocardial changes in some of the patients is mentioned, but this may be at most an additive factor.

5. The absence of cardiovascular signs and symptoms in these patients is noted, so that no clinical indications for electrocardiographic study in patients with upper respiratory infection exist.

6. Present knowledge does not allow the inference that electrocardiograms should be taken routinely during upper respiratory infection.

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Clinical Reports

COR BILOCULARE

Case Report

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Buffalo, N. Y.

COR BILOCULARE is a rare congenital cardiac anomaly and was first recorded by Wilson in 1798. Abbott, in a comprehensive study of congenital heart lesions published in 1936, recorded only fourteen examples of this anomaly. Since then, five additional cases have been reported, two of which occurred in twins.

Most subjects with this condition die in early infancy, although one patient lived to the age of 18 years. The sex distribution is about equal. There are no characteristic physical signs; no cardiac murmurs or thrills have been described. Cyanosis is the most prominent finding. Other anomalies may be associated with this condition, the commonest of which is a persistent truncus arteriosus.

CASE REPORT

On March 12, 1941, a white baby girl, weighing 8 pounds and 11 ounces, was born at the Mercy Hospital. The delivery was spontaneous from a vertex presentation under vinethene anesthesia.

The mother was 36 years of age and has five other normal children. Her past history is not remarkable. The child's father is living and well.

Immediately after delivery the child's color was good and it had a strong cry. About three hours later, it was observed that the baby became cyanotic when she cried. Examination of the infant at this time revealed no other abnormalities. No murmurs were heard over the precordium. An x-ray film showed no enlargement of the thymus gland.

For the first few days of life the baby's color was fair until it sneezed or cried; then cyanosis became pronounced. Later cyanosis became constant and was not relieved even when oxygen was given continuously. The baby had several vomiting spells with emesis of blood-streaked mucus. Its condition became progressively worse, and it expired the seventh day after birth.

Autopsy Findings.—External examination showed a well-developed and fairly well-nourished but cyanotic female infant; the only abnormality was a small angioma of the skin of the back. Examination of the internal organs revealed no important findings except in the heart.

When viewed in situ, the portion of the heart usually formed by the right auricle was seen to be slightly enlarged; the part of the left border of the heart usually formed by the left ventricle appeared more globular than usual. The pulmonary artery was in its proper position. The ductus arteriosus was present but somewhat narrow, especially in its mid-portion.

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On opening the heart only one atrial chamber was found, from which two auricular appendages projected and into which all the veins entered. The common atrium communicated through a large aperture with a thick-walled ventricle, which in turn emptied into a normal-sized aorta. Near the upper margin of the ventricle and in its anterior wall lay a small, flat, slitlike cavity which evidently was a rudimentary right ventricle. It communicated with the pulmonary artery by an opening guarded by three small but normal valve cusps. Although this chamber communicated with the large ventricle by a tiny orifice, it contained no blood and apparently did not function. This infant's heart thus had only one atrium, one useful ventricle, one rudimentary and nonfunctioning ventricle, and a small ductus arteriosus Blood entered the pulmonary artery only through this insufficient ductus arteriosus.

On more detailed examination it was found that four large veins entered the atrium. On the right side superiorly was the opening of the superior vena cava. The posterior margin of this opening was formed by a small muscular bundle, forming a semilunar ridge. This normally is the upper limbus of the foramen ovale. Posterior to and just below the orifice of the superior vena cava, the right and left pulmonary veins entered. Below these lay the opening of the inferior vena cava. This opening was partly covered by a fibromuscular membrane which most likely was the rudiment of the interatrial septum. The opening of the coronary sulcus lay between that of the inferior vena cava and the atrioventricular aperture.

Fig. 1.—The single auricle and the only functioning ventricle are shown.

The atrioventricular opening was 4 cm. in circumference and was guarded by four unequal valve leaflets, to which were attached four groups of papillary muscles.

The ventricle was as large as the combined right and left ventricles of a normal heart at birth. The thickness of its muscle wall averaged 6 millimeters. From its superior portion arose the aorta with a normal semilunar valve composed of three cusps. Just below the base of the right posterior cusp of this valve was a tiny opening in the wall of the ventricle. This tiny orifice was the only communication between the large ventricle and the slitlike cavity of the rudimentary right ventricle previously described.

The pulmonary artery was in its normal position and was guarded by three small cusps of the pulmonary valve The coronary arteries were not remarkable.

The lungs, liver, spleen, and kidneys showed passive congestion.

SUMMARY

The heart described was unusual in that it consisted primarily of only one atrium and one ventricle with a patent ductus arteriosus. The ventricle had a rudimentary slitlike cavity in its wall, but this to all intents and purposes was nonfunctioning.

This case, we feel, is a cor biloculare.

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Letters

To the Editor:

In a paper in the April, 1946, issue of the American Heart Journal (vol. 31, pp. 473 to 476) on the duration of the P-R interval and its relationship to the cycle length, the author states: "It is seen that although there appears to be a tendency for the P-R interval after exercise to be shorter, the difference is more apparent than real. For the P-R values after exercise to be significantly different from those found before exercise, a difference greater than three times the standard deviation should be present. In this series the difference was less than even twice the standard deviation." Table II (p. 476) shows in a large number of young men a mean P-R interval of 0.143 sec. and a standard deviation of 0.014 sec. before exercise, and of 0.129 and of 0.010 sec., respectively, after exercise. It is not clear whether the author refers in the section quoted to *mean* P-R values or to the P-R interval in the individual case. His own data (Fig. 1, p. 474) show definitely that the mean P-R interval is shorter at short than at long cycle lengths. This is demonstrated by the following facts: The mean P-R interval of the 189 individuals (Fig. 1) whose cycle lengths were below 0.46 sec. is 0.123 ± 0.00068 sec., and the standard deviation is 0.014 ± 0.00047 sec. The 160 individuals whose cycle lengths exceed 0.79 sec. have a mean P-R interval of 0.1475 ± 0.00091 sec. and a standard deviation of 0.017 ± 0.00064 sec. The difference between the means is 0.0247 ± 0.00114 sec., or over twenty times its probable error. (See Raymond Pearl, *Introduction to Medical Biometry and Statistics*, Philadelphia, 1930, W. B. Saunders Co., p. 283, et. seq.) Hence it is clear that the *mean* P-R interval shortens as the heart rate increases, and there is no doubt, in view of the large number of persons studied, that the figures given by the author in his Table II prove this just as conclusively as the above analysis. In contrast to these statements about the mean interval, in the *single* case among healthy male adults in the age range studied, the P-R being measured by the author's technique, the odds against the interval falling outside the range set by three standard deviations is about 370 to one.

In an earlier paper (Am. Heart J. **31**: 329, 1946) the same author states that the relationship between the Q-T interval and the cycle length is linear. In this case it is also possible to demonstrate from the data given on p. 330 that the relationship in question is actually curvilinear (Pearl: p. 386 et seq.), and this evidence becomes overwhelming when the data supplied by other authors are also treated statistically.

Richard Ashman

Louisiana State School of Medicine, New Orleans.

The following is a reply to Dr. Ashman's letter:

To the Editor:

In the section of the paper quoted (vol. 31, p. 473) and Table II (p. 476), the mean P-R values referred to are the means of all the individual P-R measurements. This was broken down into (a) the mean value of all the P-R intervals before exercise, and (b) the mean value of all the P-R intervals after exercise. Thus, a comparison was made between the P-R intervals of the same individual or group at different heart rates. However, no such comparison between individuals was made or implied by this treatment of the data. This treatment was used to indicate what the chances were for a healthy male individual chosen according to the criteria outlined in the article to show differences between P-R intervals at different heart rates greater than three standard deviations. As Dr. Ashman points out, the odds are approximately 370 to one against such an occurrence.

The second point made by Dr. Ashman, that the mean P-R interval shortens as the cycle length shortens, does not contradict any statement in the article. Not only does Fig. 1 (p. 474) show this to be true, but the coefficient of correlation that was calculated and found to be plus 0.387 shows this even more clearly. Yet, what does this mean? Showing that the P-R interval is shorter at shorter cycle lengths is only a qualitative analysis. When this is studied quantitatively by determining the coefficient of correlation it is found that, although there was such a relationship between P-R and C, the low order of magnitude of this coefficient indicates that this relationship is not of importance.

In studying the relationship of QT to cycle length (vol. 31, p. 329), Fisher's method of analysis of variance was used to determine whether or not the actual data deviated significantly from linearity. It was found that the deviation was not significant. This method was used because it was recognized as one that would give an accurate analysis of the data. Dr. Ashman applied another method of analysis to the same data. I agree with Dr. Ashman that, when this other method, the Correlation Ratio (eta) and Blakeman's Criterion, is used, there appears to be significant deviation from linearity. The question that arises is why should the same data, when analyzed by two methods, yield different interpretations. Apparently, the difference arises from the methods used. The Correlation Ratio and Blakeman's Criterion do not take into account the number of assays. A more detailed discussion of this can be found in Fisher, R. A.: *Statistical Methods for Research Workers*, ed. 6, p. 263. Because of the limitations inherent in the latter method, Fisher's method of analysis of variance was felt to be the more desirable and more accurate.

There is one point I wish to make. In analyzing the data it was realized that our data formed a regression within certain limits. Thus, we were studying only one segment of a curve or line that theoretically may extend much beyond the limits set by our study. Let us assume for argument's sake that this segment is part of a curve or even a circle. This circle may have a radius of such magnitude that the regression set by our limits forms a relatively small segment of this circle. It is known that as the ratio of segment to radius becomes smaller and approaches zero, the segment approaches a straight line. Thus, the QT/C regression studied here may be a small segment of a much greater curve, and analysis of this segment per se may fail to reveal significant deviation from linearity when only 1,400 measurements are used. However, if 14 million measurements were analyzed we might then find that the deviation from linearity which was not significant when 1,400 were studied is now significant.

Thus, although this study failed to reveal significant deviation from linearity, it is understood that the regression might still be curvilinear. For practical purposes, however, treating this data as a linear regression is adequate.

ISIDORE SCHLAMOWITZ, M.D.

Abstracts and Reviews

Selected Abstracts

Henry, G. C., and Boone, A. A.: Electrokymograph for Recording Heart Motion Utilizing the Roentgenoscope. Am. J. Roentgenol. **54:** 217 (Sept.), 1945.

Although graphic recording of the motion of the heart and great vessels has been a long-desired goal, this method has not been used extensively because of analytic difficulties in the size, clarity, and brevity of the recorded waves to be examined on the kymogram and the time-consuming nature of the analysis. The authors have developed a method which overcomes these difficulties and produces a large, beam type or electrocardiographic type of tracing on bromide paper of a chosen point of the cardiac silhouette.

Under the roentgenoscope, the diaphragm of the electrokymograph, which contains a narrow slit, is aligned at right angles to the particular portion of the heart border to be investigated. As the heart beats, its border moves back and forth across the slit, varying the intensity of the roentgen rays passing through it. If the intensity of these rays were recorded with distortion in respect to a time axis we would have an indication of the motion of this portion of the heart border. This is accomplished by a 931-A multiplier phototube, used by Morgan in his exposure meter for roentgenography. A strip of fluoroscent screen is placed directly over the photosensitive area of the 931-A tube. As roentgen rays strike the tube, the cathode is illuminated. When the shadow of the heart border moves inward (contractile motion) this strip of screen is further irradiated by the beam. Thus, the total light emitted is proportional to the changes in the position of the heart border. The current output is amplified and recorded by a galvanometer. Tracings of the carotid pulse are recorded simultaneously to align curves from separate points on the cardiac border in respect to the time relations in the cardiac cycle.

Sample records are presented which represent the motion of the left ventricular border, the pulmonary artery, the aortic knob, and the right auricular border. These are aligned, one above the other, by the carotid pulse tracing, so that events or different records falling on any given vertical line occur at the same time. The wave forms for each of the border areas of the heart are found to be characteristic of that particular area and they resemble closely the respective volumetric wave forms found in physiology texts.

These authors expect to present more detailed information regarding the individual chambers of the heart in subsequent papers. SERBER.

Dobson, C.: Subacute Bacterial Endocarditis Complicated by Pregnancy, Successfully Treated With Penicillin. Am. J. Obst. & Gynec. **51:** 427 (March), 1946.

The patient, a 24-year-old gravida ii, para O, entered the hospital Jan. 2, 1945, for a therapeutic abortion. She gave a history of having had a cold for the preceding two weeks, complicated by backache, low-grade fever, nausea, and occasional tenderness in several of the digits. She presented evidence of rheumatic mitral and aortic disease, and two blood cultures were positive for *Streptococcus viridans*. Penicillin administration was begun on Jan. 14, 1945; 200,000 Oxford units were given daily in divided doses. On January 13, the blood culture was negative. Repeated subsequent cultures were negative. After five weeks of penicillin therapy her progress was not satisfactory, and it was considered advisable to interrupt the pregnancy, which was

terminated on the nineteenth of February. The patient was discharged on March 18, 1945, nine days after penicillin was discontinued. The cardiac reserve was good, and the patient was considered to have recovered from subacute bacterial endocarditis. BELLET.

Hunter, W. S.: Coronary Occlusion in Negroes. J. A. M. A. **131:** 12 (May 4), 1946.

This author, after reviewing the literature and as a result of his own observations and experiences, concludes that the diagnosis of coronary occlusion is rarely made ante mortem in Negroes. He gives as reason for this the fact that, during the episode of coronary occlusion, dyspnea is the chief complaint and pain is absent. He reviewed a series of 1,000 consecutive autopsies on Negroes and 1,000 consecutive autopsies on white patients at the Louisville General Hospital over a ten-year period. He found that below the age of 70 years the incidence of myocardial infarction was approximately the same in both Negro and white patients. Dyspnea rather than substernal pain was the outstanding presenting symptom in all the Negroes prior to death.

Hunter stresses the point that careful clinical and electrocardiographic examination of Negroes with acute left ventricular failure will reveal many diagnoses of coronary occlusion. BELLET.

Weinroth, L. A., and Herzstein, J.: Relation of Tobacco Smoking to Arteriosclerosis Obliterans in Diabetes Mellitus. J. A. M. A. **131:** 205 (May 18), 1946.

The purpose of this study was to determine the relative incidence of occlusive arterial disease in diabetic patients who smoked, as compared with a similar group who abstained from the use of tobacco. The findings indicate the significantly higher incidence of occlusive vascular disease in diabetic patients who used tobacco as compared with diabetic nonsmokers. This held true in all decades up to 70 years. The reason for the increased frequency of occlusive arterial disease which they have observed in diabetic smokers is not clear The authors suggest that over a period of time by virtue of its vasoconstrictor effect, tobacco may cause an already constricted arteriosclerotic vessel to become still further narrowed. Such encroachment on the lumen would favor thrombus formation. A lowered frequency of arteriosclerosis obliterans prevailed in general among nonsmokers regardless of such factors as severity of the illness, adequacy of control, and the presence of obesity or hypertension. BELLET.

Bauer, G.: Heparin Therapy in Acute Venous Thrombosis. J. A. M. A. **131:** 196 (May 18), 1946.

This author differentiates between the inception and course of occlusive disease of the superficial and deep veins. In superficial veins, thrombophlebitis is the primary disorder and is followed secondarily by thrombotic obliteration of the venous segment involved. In the large deep veins of the legs the process begins with a thrombus which arises in a muscle vein and projects into the lumen of one of the large venous trunks of the lower part of the leg. Here it becomes the starting point for the deposition of a thrombus which extends upward and, in about 80 per cent of the cases, reaches the femoral vein. This process, which generally lasts about twenty-four to forty-eight hours, may result either in the formation of an embolus, or, by far the most common course, the thrombus may grow in thickness and block the lumen of the femoral vein along its entire length and produce typical phlegmasia alba dolens. Complications of this process in the chronic stage are permanent swelling of the legs, indurative lesions, and leg ulcers in a large percentage of cases. The author emphasizes the importance of early diagnosis of this condition which is suggested by the presence of tenderness in the back of the calf accompanied by mild swelling and pain in this region. The diagnosis is confirmed by phlebography which presents a rather characteristic picture. The opinion is given that phlebography should constitute a routine method of study in all cases of suspected early thrombosis. Remarkable improvement followed the early institution of heparin therapy. In addition, forceful active leg movements were instituted immediately after the diagnosis was established. The mortality from thromboembolism under this

treatment was decreased to less than one-tenth of what it formerly had been. The length of stay in bed was reduced from forty days to less than five days, and incapacitating aftereffects did not appear in the majority of cases so treated. BELLET.

Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel. III. The Physiologic and Toxic Effects of Intensive Salicylate Therapy in Acute Cases. J. A. M. A. **131:** 200 (May 18), 1946.

Following the regimen outlined by Coburn, thirty-five patients with acute rheumatic fever received daily intravenous doses of 10 Gm. of sodium salicylate dissolved in 1 liter of saline solution or Ringer's lactate solution for four to ten days. Nineteen additional patients received oral therapy throughout the course of treatment, which consisted of between 10 and 12 Gm. of acetylsalicylic acid or sodium salicylate daily, usually in conjunction with 8 Gm. of sodium bicarbonate. Under this regimen, toxic reactions of serious proportions occurred, but these were preventable in most instances. Hypoprothrombinemia occurred frequently, reaching a maximum in the first week of salicylate administration, but improved spontaneously thereafter even though large doses were continued. No instance of hemorrhage as a result of hypoprothrombinemia was observed. The alkali reserve was depleted unless adequate amounts of alkali were given in conjunction with salicylates. When large doses of salicylates were given orally, between 0.8 and 1 Gm. of sodium bicarbonate was given with each gram of salicylate. For the same reason, intravenous salicylates should be administered in Ringer's lactate solution instead of saline solution.

Severe delirium, "acute salicylism," is dependent on the rapid rise in blood salicylate levels associated with intravenous therapy and occurs most often in acutely ill patients who have not built up an antecedent tolerance to the drug. It was not observed in this series, following oral therapy.

The author found that serum salicylate levels of 25 mg. per 100 c.c. or higher have been found to suppress rheumatic infection satisfactorily. Salicylate therapy was continued until the erythrocyte sedimentation rate had been normal for two weeks. BELLET.

Bourne, G.: Bicuspid Aortic Valve Diagnosed During Life. Brit. M. J. **1:** 609 (April 20), 1946.

This author discusses criteria upon which he believes a diagnosis of bicuspid aortic valve may be made during life. These are the appearance of the signs and symptoms of subacute bacterial endocarditis and accompanying aortic insufficiency in an individual, usually young, who has previously been carefully examined and in whom there was no evidence of heart disease of any kind. Since bacterial endocarditis rarely develops upon a normal aortic valve, the sudden appearance of aortic regurgitation together with infective symptoms in a previously normal person is extremely suggestive of the presence of a bicuspid valve. The diagnosis was made in life and confirmed by necropsy in a case presented by the author. BELLET.

Lenegre, J., and Maurice, P.: Some Results of Recording Electrical Currents From the Right Auricle and Ventricle by the Direct Intracavity Lead. Arch. d. mal. du coeur. **38:**298 (Nov.-Dec.), 1945.

The authors report some of their results in electrocardiograms recorded from within the right auricle and ventricle in man. Their technique involved the use of a soft exploring electrode of tin which projects from the end of a No. 13 ureteral catheter. A gold wire in the lumen of the catheter connected the lead wire to the electrode. The catheter was inserted into an antecubital vein and, under fluoroscopic observation, was passed into the right auricle or ventricle. The indifferent electrode was placed on the left leg. The intra-auricular and intraventricular leads were recorded simultaneously with the three limb leads.

Records obtained from within the right auricle showed rapid auricular waves of considerable amplitude which were often analogous to those obtained from an esophageal lead. Records ob-

tained from within the right ventricle indicated clearly the sequence of ventricular activation in extrasystoles and in bundle branch block. Current views on the interpretation of electrocardiograms in these conditions were confirmed.

It is emphasized that electrocardiograms from the intracavity leads must be interpreted with some caution because of artefacts which are inherent in the technique. There is no certainty as to which part of the cavity wall is in contact with the electrode nor is there any assurance that the contact is constant because of the movements of the heart. Some of the resultant artefacts are obvious, but others may be less apparent. The procedure is considered valuable, however, for the study of arrhythmias and conduction defects. LAPLACE.

Pruche, A: Cardiodynamometry. A Practical Test for Determination of the Functional Capacity of the Heart. Arch. d. mal. du coeur. **38**:264 (Nov.-Dec.), 1945.

The author states that the criterion for the functional capacity of the left heart is the supply of an adequate amount of blood to the peripheral tissues in proportion to their activity, while that of the right heart is the withdrawal of an adequate amount of blood from the venous system to prevent peripheral congestion. As a test of cardiac function based on this concept, he uses the following procedure. The patient is placed in a recumbent posture with one arm held at a right angle to the body. An armlet connected to a water manometer is placed on the upper arm. A second armlet connected to a plethysmograph is placed on the lower arm. The subject rises, performs a standard exercise of twenty deep flexions of the legs, and lies down. Measurements of the circulation are made immediately. The subject then rises, makes fifty deep flexions, and again lies down, whereupon the measurements are repeated.

Three determinations are made. The first concerns the pressure in the return circulation (PV). The pressure in the upper armlet is gradually increased and a notation is made of the level at which beginning congestion in the lower arm is indicated by the plethysmograph. This is considered to be the venous pressure in the arm. The second determination concerns the systolic index (IS). At the moment of recording PV, the upper armlet pressure is rapidly increased to 80 cm. of water and the resulting upward deflection of the plethysmographic indicator for a period of exactly ten seconds is recorded. The third determination concerns the volumetric index (V). This is the relation of IS to the number of pulses noted during ten seconds from the moment of establishing the IS. It represents the volume of blood entering the distal segment of the limb.

Criteria for a normal cardiodynamic status are: For PV, constant or little variation throughout the test; for IS, in relation to its control valve, IS increases two points for the first exercise and four points for the second; for V, no significant change.

Results of the application of this test to ambulatory cardiac patients are reported. It is emphasized that a normal test does not necessarily indicate absence of organic heart disease, nor does an abnormal result indicate the existence of organic heart disease. The test affords simply a quantitative estimate of the functional capacity of the heart. LAPLACE.

Penner, S. L., and Peters, M.: Longevity With Ventricular Aneurysm; Report of a Case With a Survival Period of Fifteen Years. New England J. Med. **234**:523 (April 18), 1946.

The case is reported of a 43-year-old infantry officer who had a severe anginal attack in October, 1929. A second attack, accompanied by shock and an audible friction rub occurred in November, 1929. A third attack, also accompanied by an audible friction rub, occurred in January, 1930. The electrocardiogram showed evidence of a typical acute anterior infarction. Recovery ensued without congestive failure but the patient remained in the hospital for one year. Thereafter he led an active life and in September, 1942, he returned to the Army on limited duty. In September, 1944, he had a recurrence of moderate anginal pain and dyspnea on effort. X-ray examination showed slight cardiac enlargement and, overlying the left ventricular portion of the cardiac silhouette, a thin curvilinear band of calcification forming the outer half of a soft tissue condensation. Fluoroscopy revealed that the calcification was in the outer surface of an outpouching

of the anterior surface of the left ventricle. No pulsation in the area was noted. A diagnosis of left ventricular aneurysm with calcification of the ventricular wall was made. The patient's symptoms subsided and when last seen on Sept. 6, 1945, he was feeling well and enjoying deep-sea fishing.

It is pointed out that the aneurysm in this case had probably been present for fifteen years. The fact that the patient remained in the hospital for an entire year following his initial illness is considered responsible for the unusual degree of recovery. LAPLACE.

Stearns, S., Riseman, J. E. F., and Gray, W.: Alcohol in the Treatment of Angina Pectoris. New England J. Med. **234:**578 (May 2), 1946.

Observations were made on the therapeutic effect of alcohol in a series of twenty-one patients who had angina of effort. The series included nineteen men and two women. Their ages ranged from 39 to 75 years. Only one had had recent cardiac infarction and none had congestive failure. Control determinations were made of the patients' ability to work by subjecting them to the Standardized Exercise Tolerance Test which consists of continuously ascending and descending a two-step staircase in a cold room. The effect of alcohol was then studied by repetition of the test.

Twenty-one patients took one ounce of whisky at various times up to ninety minutes before the test. Five of the patients were able to perform from 18 to 27 per cent more work than was otherwise possible. Nine patients drank one ounce of whisky four times daily for a week prior to the test. Of these, two patients had no attacks of pain during the week but had no demonstrable increase in exercise tolerance, while in two patients, the angina became worse during the week. Five patients felt subjectively better; in one, exercise tolerance was increased 23 per cent and in another, it was decreased 33 per cent.

When one-half ounce of whisky was held in the mouth during the test in order to demonstrate a possible reflex effect, there was no change in pain or in exercise tolerance.

It is concluded that therapeutic doses of whisky do not measurably shorten the duration of attacks or increase the work capacity of patients who have angina pectoris. Many patients are afforded an increased sense of well-being but others are made worse.

LAPLACE.

Froment, R., Guinet, P., Vignon, G., and Martin-Noel: Atheromatous Coronary Disease of Early Onset and Parallel Course in Twins. Arch. d. mal. du coeur. **38:**260 (Nov.-Dec.), 1945.

Two cases are reported of homologous twins who were apparently in excellent health until the age of 34 years when, within a few weeks of each other, both began to have typical severe angina of effort. Both had mild hypertension. Nine months later, the first twin died suddenly after several days of recurrent spontaneous anginal attacks. Autopsy showed almost complete atheromatous obliteration of all the large coronary arteries together with diffuse myocardial degenerative change.

In the case of the second twin, the angina of effort persisted for several months but by the following year had disappeared completely. Three years later, angina reappeared in mild form and then suddenly a severe spontaneous attack occurred, during which the patient died. No autopsy was performed but an electrocardiogram taken two years previously had shown flat T_2 and a deeply negative pointed T_3.

These cases emphasize strongly the familial character of cononary artery disease.

LAPLACE.

Froment, R., and Gonin, A.: Aortic Stenosis Due to Calcified Syphilitic Valvulitis. Arch. d. mal. du coeur. **38:**257 (Nov.-Dec.), 1945.

Three cases are reported in which aortic insufficiency caused by syphilitic valvulitis was accompanied by a substantial degree of stenosis. Autopsy revealed that the cause of the stenosis

in all cases was secondary calcification which had involved a sufficient area of the affected valves to prevent their complete opening.

It is pointed out that aortic stenosis of sufficient degree to be recognized clinically is generally considered to be evidence against syphilis as the cause of the valve lesion. The three reported cases are cited as exceptions to this rule. It remains true that syphilis does not produce aortic stenosis but there are, nevertheless, rare instances of syphilitic aortic valvulitis in which a moderate degree of stenosis may occur as a result of partial secondary calcification of the valve leaflets.

LAPLACE.

Lium, R.: Cardiac Arrest After Spinal Anesthesia. Report of a Case With Recovery. New England J. Med. **234**:691 (May 23), 1946.

The case is reported of a 62-year-old woman who was admitted to the hospital for a cholecystectomy. No preoperative cardiovascular abnormality was noted except a blood pressure of 180/90. The preoperative medication included pentobarbital sodium, 0.2 Gm., at bedtime, which was repeated one hour before operation, and morphine sulphate, 10 mg., one-half hour before operation. Spinal anesthesia was effected by pontocaine, 18 mg. in 3 c.c. of 10 per cent glucose, placed in the subarachnoid space through the third lumbar interspace. Operation was begun eleven minutes after the administration of the anesthetic. The patient stopped breathing forty-three minutes later. A right rectus incision had been made and the heart could be palpated through the diaphragm. No impulse was detectable. Cardiac massage was immediately instituted by compressing the heart against the chest wall. With each compression the heart flickered a little more firmly and a slow spontaneous beat was suddenly established five minutes from the onset of cardiac arrest. Blood pressure immediately rose from 0 to 170/90. Periods of artificial respiration had been alternated with those of cardiac massage. Spontaneous respiration was resumed thirty-five minutes later and the operation was completed.

The patient's general response for twenty-four hours after operation was that of a decerebrate, but complete recovery occurred during the next three days. The precise mechanism of this type of anesthetic accident is undetermined. In most cases, cardiac massage and artificial respiration with pure oxygen are capable of reviving the heart.

LAPLACE.

Bridges, W. C., Wheeler, E. O., and White, P. D.: Low-Sodium Diet and Free Fluid Intake in the Treatment of Congestive Heart Failure. New England J. Med. **234**:573 (May 2), 1946.

The treatment of cardiac edema by restricting sodium and permitting a free fluid intake has not yet received wide application, although its usefulness is now generally appreciated. At the Massachusetts General Hospital, sixty-four patients who had congestive heart failure were treated by this technique as well as with digitalis, diuretics, and other routine measures. Seventeen patients obtained much help, fifteen moderate benefit, eight slight benefit, and seven no benefit. In the remaining seventeen cases, the patients were either uncooperative or the data were insufficient to warrant inclusion in the present report.

The diet used contained about 700 mg. of sodium in an amount of food equivalent to 1,800 calories. If the food tasted too flat, ammonium chloride was used in place of salt. It was essential that no salt or soda be used in cooking or included in incidental medicines.

The advantages of the treatment are that it frequently permits control of edema that cannot be controlled otherwise, diminishes the frequency with which mercurial diuretics must be given, and enables the patients to take more water. The disadvantages are the difficulty of preparing or obtaining the diet outside of a hospital and the flat taste of the food.

The optimum amount of water to be taken has not yet been determined and it is uncertain whether 5,000 to 6,000 c.c. per day is more beneficial than 2,000 to 3,000 c.c. Undoubtedly, however, the water intake formerly recommended was distinctly inadequate because diminished renal function often prevents sufficient excretion of waste products when the daily fluid intake is less than 1,500 c.c.

LAPLACE.

Bachman, A. L.: Quantitative Roentgenographic Method for the Determination of Left Auricular Size. Am. J. Roentgenol. **55**:427 (April), 1946.

The importance of roentgenographic evidence of enlargement of the left auricle in the diagnosis and management of rheumatic heart disease is at present generally accepted. The roentgenographic recognition of normal or markedly enlarged left auricles offers little difficulty. However, considerable difficulty is encountered in the diagnosis of slight enlargement of the left auricle. Much of this difficulty is due to the wide variation in the outline of the auricle in normal cases and to the absence of a sharply defined difference between the appearance of the normal and minimally enlarged auricular chamber.

The purpose of this paper is to demonstrate the amount of roentgenographic variation in the appearance of the left auricle in healthy individuals and to furnish quantitative standards establishing the distribution range for this normal variation. The anatomy of the esophagus and its relation to the neighboring structures in the anteroposterior and the oblique views is discussed in detail. At the site of the three main impressions, the aortic, the pulmonary, and the left auricular, the esophagus shows local posterior bulges but resumes its general downward and anterior direction immediately below the indentations. A short distance (0.7 cm.) below the lower end of the aortic indentation is the inconstant bronchial impression. The best indicator of the general esophageal course is the direction of the "alpha" segment, which is located below the bronchial indentation, since there are no local impressions by adjacent viscera on this portion of the esophagus. The angle which the posterior border of the opacified esophageal "alpha" segment makes with the vertical axis has been designated as "gamma" and is an index of the general esophageal course. The angle between the downward extension of the posterior border of the "alpha" segment, and the posterior margin of the esophagus in the upper portion of the auricular impression has been designated as the angle "theta."

The left auricle, as it enlarges, expands in a posterior direction early in its course; upward enlargement is usually seen shortly afterward. Posterior displacement is indicated in the early phases by an increase in the angle between the lower end of the "alpha" segment and the upper portion of the auricular impression (that is, the angle "theta").

Methods were therefore employed to yield quantitative measurements for the indices of left auricular size: (1) the angle "theta," (2) "M. P.," which is the distance from the most posterior point on the posterior border of the esophagus in the auricular region to a vertical line dropped from the most posterior point on the border of the esophagus to the region of the aortic knob indentation, and (3) the angle "gamma." A series of other measurements, namely, (a) the height and weight relationship, (b) frontal cardiac area, (c) transcardiac diameter, and (d) thoracic height, were also made and statistical correlations calculated between these external somatic factors and the three main indices.

Two hundred fifty healthy male soldiers between 18 and 30 years of age were selected following a physical examination in which rheumatic and other types of heart disease were ruled out. A set of four roentgenograms were obtained for each examinee, measurements as outlined were made, and a series of normal standards created. The views employed were posteroanterior in mid-inspiration, right anterior oblique in mid-inspiration, left lateral in mid-inspiration, and right anterior oblique in mid-expiration.

The quantitative analysis method was found not only of great aid in establishing the diagnosis of slight left auricular enlargement, but also was of considerable value in following patients where the diagnosis was made in the initial examination. In the presence of conditions which grossly alter the course of the esophagus, measurements were obviously invalid. These conditions included aneurysm of the aorta, substernal goiter, arteriosclerosis with tortuosity, mediastinal tumors, pulmonary fibrosis, and pericardial effusion. BELLET.

Gravelle, L. J., and O'Donnell, C. H.: Lumbar Sympathectomy for Chronic Leg Ulcers. Am. J. Surg. **71**:620 (May), 1946.

Twenty-one patients with chronic leg ulcers were treated by lumbar sympathectomy with good results in twenty. The ulcers were due to venous stasis, arterial disease, and trauma.

A rise in skin temperature after lumbar paravertebral block was used as a criterion in selecting patients for sympathectomy. Removal of the second and third lumbar ganglia proved satisfactory for sympathetic denervation of the lower extremity. NAIDE.

Farinas, P. L: Retrograde Abdominal Aortography. Am. J. Roentgenol. **55**:448 (April), 1946.

The author describes his technic of retrograde abdominal aortography. The patient is sedated with a barbiturate the night before and morphine is administered one hour before the procedure. Prior to injection, the femoral artery is exposed by blunt dissection under local anesthesia at the level of the triangle of Scarpa and is punctured with a trochar 1.5 mm. in diameter, through which injection of 50 c.c. of a 70 per cent solution of Diodrast is made in two and one-half to three seconds. Tourniquets must be placed at the roots of both lower extremities in order to produce a slowing of the circulation. The Trendelenburg position may be required in certain cases. To avoid changes in pressure due to inertia and cardiac systole, the author uses a specially designed pump with a piston which acts upon the embolus of the syringe. The piston works by an air compressor with a regulator and a manometer. By this means 25 c.c. of the opaque solution per second can be injected through the trochar, with a constant pressure of 15 pounds. The first roentgenogram is taken when 40 c.c. of the opaque substance has been injected and the second one immediately after completion of injection, using a fast plate changer. The trochar is withdrawn when the injection is finished, and the adventitia of the artery and wound is closed.

By this method pathologic changes in the aorta and its branches can be clearly visualized and studied. Roentgenograms are presented in cases of atheromatous degeneration of the aorta and iliac arteries, aneurysm of the abdominal aorta, uterine fibroma, ovarian cyst, and visualization of the renal circulation. By means of urograms taken at the same time, valuable information concerning renal function is obtained, and thus a method of further study of renal pathology is presented. The author hopes that retrograde abdominal aortography will become a common method of clinical investigation and diagnosis. SERBER.

Cook, W. T., Cloake, P. C. P., Govan, A. D. T., and Collbeck, J. C.: Temporal Arteritis: A Generalized Vascular Disease. Quart. J. Med. **15**:45 (Jan.), 1946.

The thesis is presented that there exists in elderly people a widespread arterial disease, not uncommon but rarely recognized, in which characteristic arterial and striking local signs occur. The inflammatory and degenerative changes in the walls of the affected arteries produce a characteristic histologic picture. The case histories of seven such patients with temporal arteritis are presented. The symptoms and signs in this group, together with those from the thirty-one cases reported in the literature, are described.

The characteristic clinical features are anorexia, loss of weight, joint and muscle pains, pyrexia, painful arterial thrombosis, and severe headaches, occurring in elderly patients. At least one-half the patients so far reported have had visual disturbances leading in many instances to complete loss of sight. Post-mortem examination was carried out in two cases. A characteristic histological picture was noted in the aorta and in the temporal, radial, subclavian, femoral, coronary, renal, retinal, coeliac, and mesenteric arteries. Involvement of the femoral vein was found in one case.

The pathological features are those of a subacute inflammation spreading probably by the vasa vasorum to the media. The internal elastic lamina appears to cause the inflammation to spread longitudinally. The lamina may be destroyed and in the process of healing, new reduplicated layers are formed. The intima becomes hypertrophied and thrombosis is a common sequel. Pathologically the vascular disease differs from thromboangiitis obliterans and periarteritis nodosa.

The prognosis is relatively good as regards life, though it may be fatal in some cases. Though the generalized character of the disease is emphasized, the term temporal arteritis has been retained as indicating a specific clinical entity in the absence of any definite etiological factor.

NAIDE.

Faust, F. L.: Repeated Sympathetic Blocks: Their Limitation and Value. Anesthesiology **7**:161 (March), 1946.

The value and limitation of repeated sympathetic blocks are emphasized. This form of therapy is useful in diseases of the arterial and venous systems, particularly in acute and chronic thrombophlebitis, post-traumatic dystrophies, traumatic shock associated with a crushing wound of an extremity, various inflammatory processes, herpes zoster, and joint stiffness. The technics of lumbar and cervical blocks are described. NAIDE.

Weeks, D. M., Steiner, A., and Victor, J.: Splenorenopexy in Essential Hypertension. Surgery **19**:515 (April), 1946.

Splenorenopexy in the dog with bilateral constriction of the renal arteries produces a collateral circulation from the spleen to the capillaries about the convoluted tubules of the renal cortex. A reduction in blood pressure occurs in hypertensive dogs following splenorenopexy. It was therefore decided to test the effects of splenorenopexy in patients with essential hypertension. The operation was performed on three patients aged twenty-four, thirty, and thirty-two years, respectively. The cut edge of the spleen was apposed to the cut surface of the kidney.

The results were uniform. In none of the patients with hypertension was the blood pressure reduced for more than three weeks. This patient was seriously ill at the time with pulmonary embolism and infarction. The other two showed a fall in blood pressure only during the operation.

It was concluded that splenorenopexy had no significant effect on the blood pressure of three patients with essential hypertension. NAIDE.

Pratt, G. H.: Traumatic Aneurysms of the Extremities. Am. J. Surg. **71**:743 (June), 1946.

Five aneurysms of the lower extremities, the result of gunshot wounds, were present in 450 wounded men. A tendency to massive hemorrhage was characteristic and in itself was an indication for operation. As a result of the author's experience, the following suggestions were made relative to the management of such patients: Where possible, the operation should be postponed for three to six months to permit adequate collateral circulation to develop, but where the wound is open or infected, delay is dangerous. Operation in such instances should be performed at the earliest opportunity where adequate instruments and surgical personnel are available. Two tourniquets should accompany transportation of such patients and should be applied, in event of severe hemorrhage, above and below the site of bleeding. Sympathetic nerve blocks are an important part of therapy and may mean the difference between success and failure in the surgical treatment. Where plastic operation on the artery has been done, the anti-coagulants heparin and dicumarol are necessary and should be continued until the outcome is no longer in doubt. After operative recovery, these patients should be treated like those with obliterative arterial disease, with emphasis on the development of collateral circulation and care to prevent injury or infection of the part. NAIDE.

Blalock, A.: Effects of an Artificial Ductus Arteriosus on Experimental Cyanosis and Anoxemia. Arch. Surg. **52**:247 (March), 1946.

Experimental studies were performed in an effort to determine whether the creation of an artificial ductus arteriosus would be helpful in the treatment of pulmonary stenosis or atresia in patients. Attempts to produce the desired degree of pulmonary stenosis were unsuccessful. It was then decided to attempt to produce unsaturation of the arterial blood by the removal of pulmonary tissue combined with the creation of a pulmonary arteriovenous fistula. This was finally done successfully by the removal of lobes of one or both lungs and the anastomosis of the severed proximal ends of the pulmonary artery and vein of these lobes. This resulted in a high degree of arterial oxygen unsaturation because some venous blood returned to the heart without having passed through pulmonary capillaries. An artificial ductus arteriosus was created by anastomosing the proximal end of the divided left subclavian artery to the side of the left pulmonary

artery in four of the experiments. In two dogs, the end of the innominate artery was anastomosed to the side of the right pulmonary artery. The creation of an artificial ductus arteriosus under these conditions usually resulted in an increase in the oxygen saturation of the arterial blood. The results of these studies strengthened the impression of Doctor Taussig that the patient with pulmonary stenosis would be improved if the pulmonary blood flow were increased and led to the development of the operation that is now performed on patients with pulmonary stenosis or atresia. NAIDE.

Gregory, R., Levin, W. C., Ross, G. T., and Bennett, A.: Studies on Hypertension: VI. Effect of Lowering the Blood Pressures of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearance. Arch. Int. Med. 77:385 (April), 1946.

The common therapeutic practice of attempting to lower the blood pressure of hypertensive patients made it advisable to determine whether such lowering of the blood pressure has any adverse influence. In view of the relationship of arterial pressure to renal filtration, the frequency with which hypertensive states are associated with pathologic changes, and the associated abnormalities which might influence arteriolar renal blood flow, it seemed especially desirable to determine whether therapeutically induced significant falls in blood pressure would affect renal function.

The methods used by these authors were as follows: inulin and diodrast clearances were determined as a control and after high spinal anesthesia was induced. This procedure was studied in ten patients with essential hypertension and in two patients with chronic glomerulonephritis. A significant fall in inulin and diodrast clearances was observed to occur in every instance in which the blood pressure fell significantly and remained low for as long as fifteen minutes. It was also observed that the degree of decrease in inulin and diodrast clearances was roughly proportional to the amount and duration of the fall of the blood pressure. That the decrease in clearance values was caused by the drop in blood pressure was shown by the following data: (1) The clearance values invariably rose toward the normal control levels during the second experimental hour when the blood pressure had risen toward or to the control level; (2) in several patients in whom the blood pressure remained low for two hours, the inulin and diodrast clearances remained proportionally low. In one patient in whom there was no fall in blood pressure although sensory paralysis had reached the second interspace, with complete motor paralysis of the lower extremities, there was a slight unexplained rise in pressure and a definite increase in clearance values.

The authors further emphasize that the correlation between the fall in blood pressure and the diminution in inulin and diodrast clearances occurs in patients with either normal or impaired renal function. They conclude that the results of this study necessitate a clinical appraisal of the effect on renal function of any therapeutic effort which aims at symptomatic lowering of the blood pressure in patients with hypertension. BELLET.

McDowall, R. J. S.: The Stimulating Action of Acetylcholine on the Heart. J. Physiol. 104:392 (April), 1946.

Acetylcholine injected into the isolated perfused hearts of cats, rabbits, and rats causes slowing and weakening of the heart beat which is almost invariably followed by an increase in rate and strength of the heart beat. Atropine abolishes the initial inhibitory effect of acetylcholine and, usually, the secondary acceleratory effect so that the only effect of acetylcholine after atropinization is a more forceable systolic contraction. Eserine enhances and ergotoxine abolishes or reverses the stimulating action of acetylcholine on the atropinized heart. After paralysis of the cardiac autonomic ganglia by nicotine, acetylcholine still exerts its stimulant effect; it must act, therefore, directly upon the cardiac muscle. After section of the A-V bundle, acetylcholine causes only a slight initial inhibitory effect upon the ventricle, followed by the usual stimulating effect.

On the basis of these data it is reasoned that the increased force of ventricular contraction during vagal slowing is not only a function of the cardiac muscle in accordance with Starling's Law of the Heart, but also a direct effect of the released acetylcholine on ventricular muscle. FRIEDLAND.

Book Reviews

ELECTROCARDIOGRAPHY: By Louis N. Katz, A.B., M.A., M.D., F.A.C.P. Lea & Febiger, Philadelphia, 1946, ed. 2.

This is the second edition of a well-known book and many obvious changes have been made in both text and illustrations. There are 825 pages with 525 excellent illustrations, a considerable increase over the previous edition. The paper stock is high grade and there are few, if any, typographical errors.

The author has changed his views on several subjects such as the range of the normal electrocardiogram and the nature of the shortened P-R, prolonged QRS syndrome. In the previous edition the precordial leads were limited to CF_2 and CF_4, while this edition includes CF_5.

Most beginners will find this book extremely complex, but an effort toward simplification has been made by listing the salient diagnostic points of each condition in concise fashion. Advanced students will find a wealth of material for study, although there may be a few controversial points which are treated according to the views of the author.

There are certain subjects which, while not of great importance, are inadequately treated. Because this is a comprehensive text, it seems unfortunate that short sections were not devoted to such subjects as an analysis of the various types of precordial leads and especially V leads. There is also inadequate discussion of extremity potentials and the esophageal lead.

Those who have used the first edition of this book will find the present edition familiar but with many improvements. Those who are unfamiliar with the work will find it a very satisfactory and comprehensive treatise. In a field which is expanding and changing as rapidly as electrocardiography, it is obviously a Herculean task to produce such a book. Readers will find it superior to most texts in this field. SCOTT BUTTERWORTH.

EXERCISES IN ELECTROCARDIOGRAPHIC INTERPRETATION: By Louis N. Katz, A.B., M.A., M.D., F.A.C.P. Lea & Febiger, Philadelphia, 1946, ed. 2.

This book is a companion volume to the author's text on Electrocardiography. It includes 100 cases illustrated with 166 electrocardiograms and brief case histories. A number of new cases have been substituted in this edition and the total number of cases has been expanded from 90 to 100.

It is obviously difficult in selecting cases for a volume of this type to be comprehensive, but the author has selected a variety of types which cover the more common electrocardiographic variants and abnormalities, and he has wisely omitted complex or controversial cases. All of the electrocardiograms include Leads CF_2 and CF_4 in addition to the limb leads, and most also have CF_5. An attempt has been made to include normal variants to illustrate the changes due to the position of the heart in the chest and other factors.

Embryo cardiologists will find this a very helpful book for training themselves in interpretation of "unknowns." More advanced students will find it a stimulating review which will allow them to study the views and interpretations of the author carefully. SCOTT BUTTERWORTH.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.